



Location of Recurrence by Gallium-68 PSMA-11 PET Scan in Prostate Cancer Patients Eligible for Salvage Radiotherapy

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OBJECTIVE	To identify locations of recurrence after radical prostatectomy (RP) with prostate-specific antigen (PSA) <2 by Gallium-68 prostate-specific membrane antigen (PSMA)-11 Positron Emission Tomography (PET) imaging, and to determine whether standard nodal radiation fields would cover the location of prostate cancer recurrence.
MATERIALS AND METHODS	We performed a retrospective review of patients with PSMA-PET imaging for biochemical recurrence following RP with PSA ≤2.0 ng/mL and assessed if the recurrent disease was within standard radiation target volumes. We compared patient and clinical variables between men with recurrences covered by standard salvage radiation fields and those with recurrences outside of standard fields.
RESULTS	We identified 125 patients for study inclusion. The median PSA at imaging was 0.40 ng/mL (interquartile range 0.28-0.63). PSMA-avid disease was found in 66 patients (53%). Of these, 25 patients (38%) had PSMA-avid lesions found outside of the pelvis, 33 (50%) had lesions confined to the pelvic lymph nodes and prostate bed, and 8 (12%) men had PSMA-avid recurrence only in the prostate bed. Salvage radiation including standard Intensity Modulated Radiation Therapy (IMRT) pelvic nodal volumes would not cover PSMA-avid nodal disease in 38 men (30%). PSA at the time of imaging was statistically associated with having PSMA-avid disease outside of standard nodal fields ($P < .01$).
CONCLUSION	The ⁶⁸ Ga-PSMA-11 PET detects disease in a majority of patients with PSA ≤2.0 following RP. Nearly one-third of men had PSMA-avid disease that would be missed by standard radiation fields. This imaging modality may dramatically impact the design and use of post-RP salvage radiotherapy. UROLOGY 129: 165–171, 2019. © 2019 Elsevier Inc.

Biochemical recurrence (BCR) after radical prostatectomy (RP), defined by the American Urologic Association (AUA) as prostate-specific antigen (PSA) ≥0.2 ng/mL on 2 separate occasions, and rising thereafter, occurs in 30%-60% of patients with clinically localized prostate cancer.^{1,2} Depending on clinical and histopathologic features, BCR can occur from months to

years after RP. Clinically evident disease progression often follows BCR.

Radiation therapy (RT), given in the adjuvant or salvage setting, is the primary treatment in BCR after RP, and is potentially curative in select patients, namely those with low PSA and Gleason scores.^{3,4} Several randomized trials have demonstrated the benefit of adjuvant RT, with regard to progression-free survival, in patients at high risk for relapse.^{5,6} Early salvage radiotherapy is now recommended by the AUA, and recent studies demonstrate improved biochemical progression-free survival and distant metastasis-free survival with earlier initiation of salvage radiation, even at PSA levels lower than 0.2 ng/mL.^{7,8} Importantly, salvage radiotherapy has also been shown to improve progression-free survival in patients with limited metastatic disease.^{8,9} Postoperative radiation fields primarily target the prostatic fossa and seminal vesicles, as most recurrences are classically thought to be within the perianastomotic region or retrovesical space.^{10,11} There are ongoing studies of pelvic nodal

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Financial Disclosure: There are no financial disclosures or funding to support this project. Authors responsible for statistical analyses: Lauren Boreta, Adam Gadzinski, and Susan Wu.

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Submitted: September 10, 2018, accepted (with revisions): December 10, 2018

irradiation in the salvage treatment, but nodal treatment is not consistently used in this setting.¹² Inclusion of nodal volumes is determined by clinical and pathologic factors, and is typically reserved for patients with high-risk disease, risk of lymph node (LN) involvement >15%, or evidence of nodal involvement by pathology or imaging (conventionally computed tomography [CT] or magnetic resonance imaging [MRI]).^{11,13} Dose to the prostatic fossa postoperatively is commonly 64.8-72 Gy in 1.8-2 Gy daily fractions, depending on margin status. Elective nodal volumes are treated to 45 Gy in 25 fractions, and involved nodes are treated to higher doses, dependent on bowel tolerance.¹⁴

Localization of relapsed disease, either local-regional recurrence or distant metastasis, is of practical importance in determining appropriate therapy. However, defining the site of failure in patients with PSA <2.0 ng/mL is challenging, as imaging techniques such as sodium fluoride (NaF) Positron Emission Tomography (PET), technetium-99 bone scan, choline-11 PET, and MRI lack sensitivity at low PSA levels.¹⁵ Gallium-68 (68Ga) prostate-specific membrane antigen (PSMA)-11 PET imaging has emerged as a highly sensitive modality to detect PSA secreting cells in men with prostate cancer, and has been shown to detect cancer in up to 80% of patients with PSA <2.0 ng/mL.^{15,16}

In this study, we used 68Ga-PSMA-11 PET to identify recurrence patterns in patients with PSA values \leq 2.0 ng/mL following RP, and assessed whether the location of recurrence would be covered within standard salvage (prostate bed only) or standard nodal radiation fields.

MATERIALS AND METHODS

This study was approved by the local institutional review board, and performed under an Investigational New Drug application for 68Ga-PSMA-11 (clinical trials NCT02611882 and NCT02918357). All patients provided written informed consent. Retrospective chart review was performed for patients enrolled in these prospective clinical trials from 2015 to 2017 to identify RT naïve patients that underwent imaging for BCR following RP with detectable and rising PSA \leq 2.0 ng/mL. Patients with previous exposure to androgen deprivation therapy and patients with prior radiation treatment were excluded from this analysis. Patient demographics, pathologic variables, and PSA values were recorded.

Imaging Methods

The 68Ga-PSMA-11 was synthesized as previously reported, and 3-7 mCi were injected prior to PET imaging.¹⁷ Patients were imaged using either PET/CT (Discovery VCT; GE Healthcare, Waukesha, WI) or PET/MRI (3.0-T time-of-flight Signa PET/MRI) based on referring clinician preference. Imaging occurred 55-70 minutes after injection of the radiotracer, and imaging began in the pelvis, with acquisition parameters that have been previously published.¹⁷ Pathologic confirmation of metastatic disease was not required for inclusion into the study.

Data Analysis

PSA doubling time (PSAdt) was calculated using the Memorial Sloan Kettering Cancer Center PSAdt calculator for patients

who had BCR and a rising PSA.¹⁸ Scans of patients with positive LNs identified on PSMA-PET by a board-certified radiologist were reviewed by a resident and attending radiation oncologist pair at our institution using MIM software (version 6.4.9, MIM Software Inc., Cleveland, OH) to determine whether involved nodes would be covered in traditional pelvic nodal clinical target volume as outlined by the Radiation Therapy Oncology Group consensus guidelines.¹⁹ In keeping with these guidelines, we defined pelvic LN as those below the bifurcation of the aorta (ie, common iliac, internal iliac, external iliac, obturator, presacral, and perirectal regions). We defined extrapelvic disease as PSMA-avid lesions outside of the prostate bed and pelvic LN regions (eg, inguinal LN, para-aortic LN, and any bone lesion). We then determined the proportion of patients with at least 1 PSMA-avid LN outside of standard RT fields or any extrapelvic PSMA-avid lesions. We considered patients with no sites of PSMA-avid disease to have all areas of disease covered by standard RT fields.

Statistics

We performed statistical analyses with R (Version 3.4, Vienna, Austria). Descriptive statistics were used to characterize clinicopathologic variables of interest (eg, PSA, PSAdt, Gleason score, and pathologic stage). Mann-Whitney *U*, chi-squared, and Fisher's exact tests were used to compare these variables between patients with PSMA-avid disease outside of salvage RT fields and those who had all visible disease covered by salvage RT fields. We then performed logistic regression to assess if clinical or pathologic variables were associated with a patient having PSMA-avid disease outside of standard RT fields. For multivariable analysis, we a priori planned to include clinical variables associated with high risk for recurrence according to ASTRO/AUA guidelines¹¹ (pT3, positive surgical margins) in addition to N stage, Gleason score, PSA, and PSAdt. All tests were 2-sided and *P* values <.05 were considered statistically significant.

RESULTS

We identified 125 patients for study inclusion. The median PSA at the time of PSMA imaging was 0.40 ng/mL (interquartile range 0.28-0.63, Table 1). Time to biochemical failure, or first rising PSA after prostatectomy, ranged from 2.3 to 72.1 months. The mean number of nodes removed at the time of surgery was 8.8 (range 0-45). Twenty men had positive LNs at the time of prostatectomy, 76 had pathologically uninvolved nodes, and 29 did not have an LN dissection. PSMA-avid disease was identified in 66 of 125 patients (53%). For 25 of these 66 men (38%), at least 1 extrapelvic lesion was found, including 17 of 66 men (26%) with bone metastasis (eg, Fig. 1). PSMA-avid disease was found in the pelvic LNs of 47 of 66 men (71%); the median largest LN size was 0.7 cm (interquartile range 0.5-1.0); 48 of these 66 men (73%) had all LN <1.0 cm. Of the men with PSMA-avid disease in the pelvic LN, 14 also had extrapelvic lesions; thus, 33 of 66 (50% of men with any PSMA disease) had PSMA-avid lesions confined to the pelvic LNs \pm the prostate bed. We identified 15 of 66 men with PSMA-avid recurrence in the prostate bed, but only 12% (8 of 66) of men with PSMA-avid disease, and 6% (8 of 125) of the entire cohort had disease confined to the prostate bed.

In men with PSA <0.5, 50% (42 of 84) had PSMA-avid disease, and 76% of those (32 of 42) had disease outside the prostate bed. Of those who received biopsy of the PSMA-avid

Table 1. Patient characteristics

	All	Lesion Outside of RT Field	RT Covers All Visible Disease	P Value
Number of patients	125	38	87	
Age at PSMA, median (IQR)	69.0 (63.4-72.0)	69.3 (61.7-71.0)	68.8 (63.7-72.1)	.71
PSA (ng/mL) at PSMA	0.40 (0.28-0.63)	0.53 (0.32-1.15)	0.38 (0.26-0.53)	<.01*
Months from RP to PSMA	25.1 (7.8-72.6)	16.0 (5.6-74.8)	26.9 (11.8-71.1)	.20
RP Gleason group, n, (%) [†]				.52
1 (3+3)	9 (7%)	2 (5%)	7 (8%)	
2 (3+4)	41 (34%)	10 (26%)	31 (37%)	
3 (4+3)	33 (27%)	13 (34%)	20 (24%)	
4 (4+4)	6 (5%)	3 (8%)	3 (4%)	
5 (≥4+5)	33 (27%)	10 (26%)	23 (27%)	
RP T stage, n, (%) [‡]				.64
pT2	52 (43%)	13 (36%)	39 (46%)	
pT3a	53 (44%)	19 (53%)	34 (40%)	
pT3b	15 (12%)	4 (11%)	11 (13%)	
pT4	1 (1%)	0 (0%)	1 (1%)	
RP N stage, n, (%) [‡]				.52
pNx	28 (23%)	8 (22%)	20 (23%)	
pN0	77 (63%)	21 (58%)	56 (65%)	
pN1	17 (14%)	7 (20%)	10 (12%)	
Positive margins, n, (%) [§]	37 (30%)	15 (41%)	22 (26%)	.10
Time to BCR, months	20.7 (2.7-72.1)	12.8 (2.3-59.8)	25.5 (6.6-72.1)	.22
PSA doubling time, months [¶]	8.3 (2.8-20.1)	9.7 (2.5-27.6)	7.1 (2.8-14.4)	.16

BCR, biochemical recurrence; PSMA, prostate-specific membrane antigen; RP, radical prostatectomy; RT, radiation therapy.

Percentages may not add exactly to 100% due to rounding.

* Statistically significant.

[†] Excludes 3 patients with missing data.

[‡] Excludes 4 patients with missing data.

[§] Excludes 2 patients with missing data.

^{||} Excludes 9 patients that underwent PSMA-PET prior to BCR.

[¶] Excludes 19 patients without BCR or insufficient data for calculation.

lesions, 4 were found to be true-positive metastases, and 7 were found to be false positives.

In total, 104 anatomic sites had PSMA-avid disease across the 66 men with positive PSMA scans, and 44 of 104 (42%) of these sites were outside of salvage RT fields (Table 2, eg, Fig. 2). Thirty-eight men (30%, 38 of 125 of study cohort, 58% [38 of 66] of those with PSMA-avid disease) had at least 1 PSMA-avid site of disease outside of salvage RT fields. These men had a higher PSA at the time of PSMA scan than those who had all visible disease covered by RT fields (0.53 vs 0.38, $P < .01$). Otherwise, we found no statistical difference in clinicopathologic variables between these groups of men (Table 1).

Finally, logistic regression revealed that only PSA level was associated with a patient having a PSMA-avid lesion outside of standard RT fields. This included our univariable analysis (odds ratio 4.2, 95% confidence interval 2.0-13.8, $P < .01$), and in our a priori multivariable model (PSA odds ratio 6.6, 95% confidence interval 2.0-26.1, $P < .01$) that also included pathologic T stage, surgical margins, pathologic N stage, Gleason score, and PSAdt (Supplementary Table 1). Figure 2 demonstrates the relationship between PSA, the furthest extent of PSMA-avid disease per patient, and if all PSMA-avid lesions were covered by standard salvage RT fields. With increasing PSA, a higher proportion of men had PSMA-avid extrapelvic disease and disease not covered by RT fields.

DISCUSSION

The current study confirms that ⁶⁸Ga-PSMA-11 PET imaging can localize prostate cancer recurrences in

patients with BCR after RP with PSA ≤ 2.0 ng/mL. Of our entire cohort, 30% (38 of 125) of patients had PSMA-avid disease had lesions that would not be covered by standard radiation fields. Similarly, of those patients with PSMA-avid disease, 58% (38 of 66) had lesions that would not be covered by salvage RT fields. Six percent (8 of 125) had PSMA-avid disease confined to the prostatic fossa.

The results presented here demonstrate local, regional, and distant recurrences in patients with low PSA. It is notable that we did not find an association with PSAdt, which has previously been shown to predict extrapelvic disease.²⁰ Previous studies have demonstrated that even at low PSA, patients with pT3 stage or greater have worse outcomes after salvage treatment.²¹ One potential reason is that the radiation is not appropriately targeted, and the routine use of PSMA-PET for treatment planning in salvage setting could lead to better disease-free survival following RT. In this study, 14% (17 of 125) of men had bone metastases and only 6% (8 of 125) had PSMA-avid disease confined to the prostate bed. This is in contrast to the pattern of failure analysis based on the Southwest Oncology Group (SWOG) 8794 cohort, which showed predominately local failure. In light of the present results, the bone scans utilized in the SWOG analysis may not have been able to identify the true extent of disease.²² Our results also show limited metastatic disease in patients with low PSA, which may be amenable to ablative

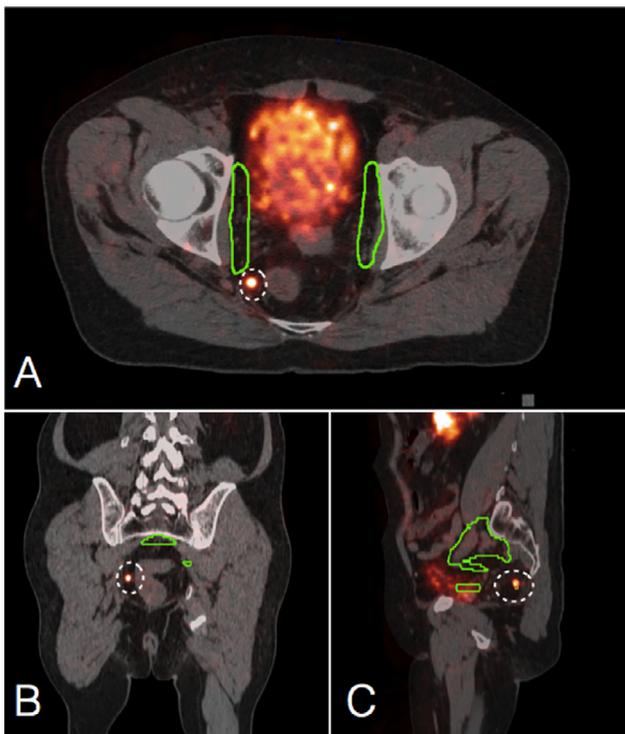


Figure 1. PSMA-avid perirectal node with overlaid nodal clinical target volume (CTV; green) contours per Radiation Therapy Oncology Group consensus guidelines. This node would not be included in standard CTV. (A) Axial CT with PSMA-PET fusion. (B) Coronal PET/CT fusion. (C) Sagittal PET/CT fusion. This patient had PSA 0.83, PSA doubling time of 1.7 months, and was 14.4 months from prostatectomy at the time of imaging. (Color version available online).

treatment. The understanding of the oligometastatic state is evolving, with many clinicians choosing to treat oligometastatic disease with curative intent.^{23,24} Metastasis-directed therapy is becoming increasingly common, with recent trial data supporting the use of SBRT and ablative radiation doses in men with limited metastatic disease.²⁵ Increased detection of metastatic disease by PSMA-PET will likely increase this practice, and prospective studies are needed to demonstrate clinical benefit.

Furthermore, we demonstrate that traditional salvage RT treatment fields would not cover many sites of recurrence. Early salvage therapy has been shown to improve survival outcomes, and we postulate that targeting treatment to the areas of involved disease by 68Ga-PSMA-PET would lead to even greater improvements in outcome. The nodal disease detected in our study was commonly smaller than traditionally used size criteria for positivity on CT or MRI (1 cm). Several groups have reported on the use of PSMA-PET in RT planning, leading to extended fields, nodal boosts, or inclusion of metastases that were not otherwise detected.^{26,27} A recent pilot study from Memorial Sloan Kettering Cancer Center (MSKCC) demonstrated that aggressive multimodal treatment in patients with limited metastatic disease can

Table 2. Sites of PSMA-avid disease

Anatomic Location	PSMA-Avid Disease	PSMA-Avid Disease Outside of RT Field
All	104	44
Prostate bed	15	0
Pelvic LN	60	15
Common iliac	7	0
Internal iliac	12	0
External iliac	16	2
Pelvic sidewall	11	0
Perirectal	11	11
Presacral	3	2
Extrapelvic LN	10	10
Inguinal	2	2
Retroperitoneal	6	6
Mediastinal	1	1
Supraclavicular	1	1
Bone	18	18
Pelvic bone	12	12
Spine	1	1
Ribs	3	3
Extremities	2	2
Viscera	1	1
Subdiaphragmatic	1	1

LN, lymph node; PSMA, prostate-specific membrane antigen; RT, radiation therapy. Each patient may have >1 or more site of disease.

achieve cure or long-term remission.⁹ Routine use of PSMA-PET in the early salvage setting may lead to better outcomes in via improved targeting and potential dose escalation, and prospective evaluation is warranted.

Our study is limited mainly in its retrospective design and that this cohort of patients was not explicitly referred for salvage RT. We also did not require patients to have negative conventional imaging; however, given the low median PSA of 0.40 and study restriction of PSA ≤ 2.0 ng/mL, we suspect that many patients would have had negative conventional imaging. The PSMA-positive lesions were not biopsy proven in all cases, and our conclusions are thus based on imaging findings alone. There are notable cases of false-positive lesions in the literature,²⁸ and biopsy is recommended for any suspicious site prior to treatment. We also considered patients with negative PSMA imaging to have all sites of disease covered by standard RT fields. As a result, patients with micrometastatic sites of disease may have been misclassified. These limitations notwithstanding, our findings may offer some explanation as to why some patients recur following salvage RT. Future prospective trials are needed to determine the appropriate incorporation of PSMA findings into salvage radiation treatment planning and if patients derive meaningful benefit from this imaging modality.

CONCLUSION

The 68Ga-PSMA-11 PET delineates disease in a majority of patients with PSA ≤ 2.0 following RP, and nearly one-third of men had lesions outside of standard nodal fields.

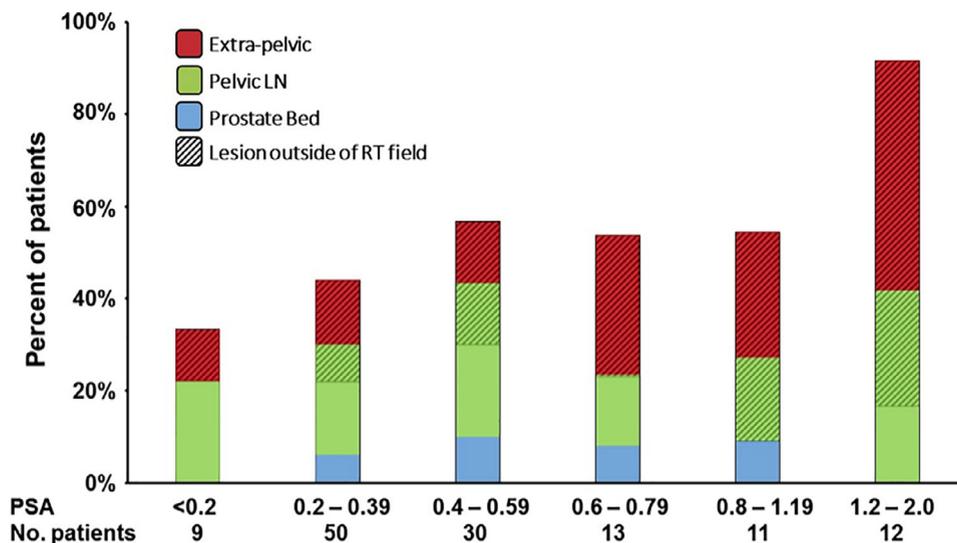


Figure 2. Distribution of the most distant site of PSMA-avid disease in each patient by PSA at imaging. Diagonal lines overlying each bar represent the proportion of patients with PSMA-avid lesions not covered by salvage RT fields. LN, lymph node; RT, radiation therapy. (Color version available online).

This imaging study provides valuable information not reflected by PSA level or kinetics, which are typically used to assess clinical risk after RP. PSMA-PET has the potential to dramatically influence post-RP salvage radiotherapy, as a significant amount of visualized disease would not be covered by standard fields. Using ⁶⁸Ga-PSMA-11 PET to detect subclinical disease has promising potential to impact clinical decision making, and prospective evaluation is warranted.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at <https://doi.org/10.1016/j.urology.2018.12.055>.

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EDITORIAL COMMENT



We appreciate the thoughtful editorial comment in regards to our manuscript.¹ Although it is true that just over 50% of patients included in our study demonstrated prostate-specific membrane antigen (PSMA) Positron Emission Tomography (PET) avidity, this is actually a fairly high percentage given the population study. Inclusion of patients was limited to those with a prostate-specific antigen (PSA) <2.0 ng/dL, resulting in median PSA of 0.4 (0.28-0.63). PSMA PET sensitivity has been shown to be dependent on PSA levels and kinetics, and is associated with higher risk disease.² Therefore, this population with a low PSA will inherently result in lower detection rates.

It is also noted that while 53% of patients exhibited positive findings on PSMA PET, only 20% of our population was found to have disease outside the salvage radiation fields. It is critical to recognize, however, our standard radiation targets included the prostatic fossa and pelvic lymph nodes. Salvage radiation historically is limited to the prostate bed alone. In our study, just 12% (15 of 125) of patients had PSMA detectable disease in the prostatic fossa, and 48% (60 of 125) had pelvic lymph nodes, meaning a majority of our cohort would have been insufficiently treated with traditional salvage radiation fields. Preliminary results of RTOG 0534/SPPORT trial demonstrated significantly improved 5-year freedom from progression when including

pelvic nodes in salvage radiotherapy, although still nearly 20% of patients progressed despite this treatment.³ One could posit that salvage RT in these cases is missing some gross disease at the time of treatment, and that treatment of all sites of disease in these 20% of patients with PSMA avidity outside salvage RT fields could lead to improved outcomes. Furthermore, PSMA-avid nodes at our institution are dose-escalated,⁴ so the imaging study would lead to management changes for men with disease within nodal volumes.

It is important to note that while Gallium-68 PSMA-11 PET is an exciting and novel imaging technique, it is not yet FDA approved. Alternative nuclear imaging agents such as F-18 fluciclovine and C-11 choline have been approved for use in biochemical recurrence, with much lower demonstrated sensitivity and specificity compared to PSMA PET.⁵ Furthermore, while false positives are a limitation of any imaging modality including PSMA PET, trained readers do not interpret celiac ganglia or other known anatomic aberrations as positive.

We do not yet know if changes to radiotherapy plans based on PSMA PET imaging will improve clinical outcomes (eg, time to biochemical failure, development of distant metastases, or overall survival). Prospective study of this modality in both the salvage and definitive setting is needed. In the era of precision medicine, just as genomic examination is being utilized to tailor prostate cancer treatment, PSMA PET imaging has the potential to lead to personalized treatments with superior outcome.

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<https://doi.org/10.1016/j.urology.2018.12.056>
UROLOGY 129: 170, 2019. © 2019 Elsevier Inc.

AUTHOR REPLY



The authors performed a retrospective study on 125 patients who experienced a biochemical relapse following radical prostatectomy (RP) and who were subjected to a PSMA-PET/CT in order to assess if the recurrent cancer foci were located within standard radiation target volumes.¹ According to their data, 53% of the

patients demonstrated PSMA-positive foci of which 25 lesions were located outside of the small pelvis. The authors concluded that the use of PSMA-PET/CT would have a dramatic effect on the design and the use of salvage radiation therapy.

Although the approach described by the authors is very innovative as might be used in individual cases, we should be cautious to be too overexcited with the use of PSMA-PET/CT and we should avoid drawing the wrong conclusions which might have a negative impact on the oncological treatment of a given patient.

We have to notice that only 66 of 125 patients (53%) exhibited positive PSMA-PET/CT signals underlining the fact 50% of patients underwent an expensive examination without a therapeutic impact. Furthermore, only 25 of 66 patients (38%) or 25 of 125 patients (20%) demonstrate potentially metastatic foci outside the boundaries of standard radiation fields. On the bottom line, only 20% of 125 patients had some type of benefit from the new imaging study. Similar data have been published recently in a cohort of 270 patients of whom PSMA-PET/CT would have changed the radiation plan in only 19% of men.²

Furthermore, we know that not all PSMA-positive lesions are due to metastatic disease.³ There could be many false-positive results due to inflammatory responses, celiac ganglia, etc. In fact, 7 of 11 patients (73%) of the current cohort demonstrated false-positive results when a biopsy of the suspicious areas was analyzed.

Although PSMA-PET/CT represents an innovative imaging modality to identify small metastatic lesions with a high diagnostic accuracy, it should only be used if it results in therapeutic consequences for the individual patient.⁴ In my view, clinical and pathohistologic parameters such as prostate-specific antigen (PSA) doubling time (PSAdt), time from RP to PSA progression, Gleason score of the RP specimen, and the presence of pelvic lymph node metastases at the time of RP need to be taken into consideration to define a risk group with a high probability of extrapelvic disease in whom a PSMA-PET/CT might be helpful to individualizing salvage therapy.

In this context, it is quite surprising that PSA-DT had no impact on the presence and frequency of extrapelvic metastases as has been reported by other groups. Verburg et al⁵ analyzed 155 patients with biochemical failure following RP and the PSMA-PET/CT was positive in 44%, 79%, and 89% of patients with PSA levels of ≤ 1 , 1-2, and ≥ 2 ng/mL, respectively. A shorter PSA-DT was significantly associated with pelvic lymph node ($P = .026$), extrapelvic lymph node ($P = .001$), bone ($P < .001$), and visceral ($P = .041$) metastases. A high Gleason score was associated with more frequent pelvic lymph node metastases ($P = .039$). In multivariate analysis, both PSA and PSAdt were independent determinants of scan positivity and of extrapelvic lymph node metastases. PSA-DT was the only independent marker of bone metastases ($P = .001$). Of 20 patients with a

PSA-DT < 6 months and a PSA ≥ 2 ng/mL, 19 (95%) had a positive scan and 12 (60%) had M1a disease. Of 14 patients with PSA < 1 ng/mL and PSAdt > 6 months, only 5 (36%) had a positive scan and 1 (7%) had M1a disease.

In summary, PSMA-PET/CT should not be overused and overinterpreted in men with biochemical relapse following RP. Clinical and pathohistologic parameters have to be taken into consideration. Until the results of prospective randomized trials are available and taking into account the pitfalls, costs, and low evidence, PSMA-PET/CT might only be helpful in men with high risk of extrapelvic relapses.^{6,7}

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<https://doi.org/10.1016/j.urology.2018.12.057>

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