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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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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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