



AUTHOR REPLY

We greatly appreciate the thoughtful comments in regards to our manuscript, which highlight a number of important issues about the use of PSMA-PET. It should be noted at the outset that PSMA-PET should not be considered a standard imaging modality. In the United States, PSMA-PET is investigational and is not FDA approved. Although PSMA-PET may be considered standard of care in a few countries, its use in the United States is limited to clinical trials. Nonetheless, the prevalence of PSMA-PET is likely to increase in the next few years, as we should be close to approval of this agent in the coming year. Our hope is that the preliminary data presented in our manuscript may help guide the use of PSMA-PET imaging.

PSMA-PET scans were available to patients meeting certain high-risk criteria prior to definitive treatment (as outlined in the manuscript) or in the setting of biochemical recurrence. We do not routinely obtain repeat PSMA-PET scans following radical prostatectomy (RP) prior to adjuvant radiation; unfortunately we are not able to verify if all PSMA-avid lymph nodes were removed at the time of lymph node dissection (LND) in our cohort. However, from our data we can tell that patients with PSMA-avid lymph nodes had more extensive LNDs (median 31 vs 17 lymph nodes removed, $p = 0.009$).

Table 1 demonstrates the cohort of patients who underwent prostatectomy prior to salvage RT. Four of the patients had negative PSMA-PET scans and negative nodes at surgery. In our cohort, median PSA after RP was 0.14 ng/mL (interquartile range 0.09-0.43). The estimated sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) in this cohort was 63%, 83%, 80%, and 56% respectively. Other institutional series with histopathologic correlates have estimated higher sensitivity and NPV¹⁻³, though lower sensitivity has also been reported.⁴ One reason for the difference between our small cohort and the literature is that there is a bias in our study, as patients with PSMA-avid nodes that were not removed at time of

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Table 1. Nodal status on PSMA-PET, postop PSA, and pathologic characteristics of the 14 patients who underwent radical prostatectomy after PSMA-PET scan

Patient Number	Nodal Status Based on PSMA-PET (Number of Nodes Identified)	Pathologic Nodal Status	Number of Pathologically Involved Lymph Nodes	Number of Lymph Nodes Removed	Max Dimension of Pathologically Involved Nodes (NA if pNO)	Postop PSA
1	–	+	3	21	9 mm	0.15
2	–	–	0	18	NA	0.04
3	–	+	1	27	4 mm	0.09
4	+(2)	+	2	39	10 mm	0.16
5	–	–	0	11	NA	0.77
6	+(4)	+	5	28	7 mm	0.50
7	–	–	0	14	NA	0.08
8	–	–	0	10	NA	0.04
9	–	+	5	29	6 mm	0.13
10	–	–	0	6	NA	0.11
11	–	+	2	17	6 mm	0.09
12	+(2)	+	3	31	18 mm	0.41
13	+(4)	–	0	34	NA	1.84
14	+(2)	+	2	22	3 mm	0.40

RP were referred for RT, thereby increasing the number of false negative lesions in our cohort.

It is important to note that in the 3 patients with pathologic lymph node involvement not identified on PSMA-PET, involved lymph nodes measured 7 mm or less (Table 1). This suggests, there is a limit to the resolution of PSMA-PET imaging, which may be technique dependent; prior data has suggested that the average size of missed lymph nodes on PSMA-PET may be smaller than what was seen in our cohort at <3 mm.¹ Further pathologic findings are in Table 1.

We also acknowledge that the Roach formula has limitations, and was validated at a time when surgical and diagnostic techniques were very different.^{5,6} We include this method of estimating lymph node involvement solely to help readers understand what guides the decision to treat pelvic lymph nodes at our institution; this is not universal practice, and remains the topic of great debate in the field of radiation oncology as we await the results of RTOG 0924.

We agree that further outcomes-driven data is required to evaluate the impact of PSMA-PET imaging. Subsequent research should be prospective, and in the context of multi-institutional cooperative groups, with adequate power and follow-up to detect clinically meaningful outcomes. These randomized trials will be imperative to perform, but difficult to accrue to once PSMA-based radiotracers become widely available.

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