EDITORIAL

Is PSMA PET disrupting traditional prostate cancer staging and treatment?

There has been a significant increase in the use of molecular imaging in the management of prostate cancer. While a number of newer radiotracers are now available, the prostate-specific membrane antigen (PSMA) based PET agents, such as 18^{F}-DCFPyL, 18^{F} flotufolastat and 68^{Ga}-PSMA-11, have become common place in the initial staging and follow up of men with high risk prostate cancer. To provide more precise anatomic localization, PSMA-PET is usually performed using image fusion along with a CT or MRI (PET/CT or PET/MRI). PSMA-PET scans can identify cancer within the prostate, and sites of metastasis including osseous, nodal, and visceral that may escape detection using standard imaging. In support of the use of these agents, the National Comprehensive Cancer Network (NCCN) guidelines suggest that PSMA-PET can be used in place of standard imaging for initial staging and with biochemical recurrence following definitive local therapy.

There have been multiple direct comparisons of PSMA-PET and conventional imaging using CT, MRI or bone scan. This radionuclide based imaging technology significantly outperforms the conventional approach to staging prostate cancer with only an occasional metastasis not being PET avid.[1]

This improvement also leaves us with a dilemma. An extensive number of clinical trials across all stages of prostate cancer completed to date have defined our current treatment approaches. These trials, with few exceptions, have relied on standard imaging for staging and follow up. PSMA-PET detection rates for biochemical recurrence following radical prostatectomy can be up to 60% with a very low PSA of < 1.0 ng/mL, far below the threshold of detection by standard CT or MRI. In men treated with radiation for localized disease, PSMA-PET can demonstrate extraprostatic disease in a third of men with a very low post treatment PSA of < 2.0 ng/mL. Below are highlighted a few examples of how PSMA-PET may disrupt our modern interpretation and application of completed clinical trials.

Non-metastatic castrate resistant prostate cancer (nmCRPC or M0 disease) is defined as a rising PSA with a castrate level of testosterone and negative conventional imaging. Several medications have been approved for these patients with rapid PSA doubling times such as apalutamide, enzalutamide and darolutamide. These trials, relying on standard imaging (SPARTAN, PROSPER and ARAMIS), have shown these agents can significantly delay the onset of metastasis and reduce the risk of death. However, using PSMA-PET imaging in this similar M0 population, most patients presumed to be M0 are actually M1 with identified metastasis and with implications for their treatment.[2]

There is growing interest in the management of oligometastatic prostate cancer. While definitions vary, oligometastatic disease is traditionally defined by routine imaging (bone scan and CT/MRI) as having a limited number of metastatic sites. The number of metastasis cited is typically less than 5 lesions. The identification of oligometastatic prostate cancer is often considered an intermediate step between limited disease and more widespread cancer. The presence of oligometastatic prostate cancer has significant prognostic and therapeutic implications for patient care. Once again, when using PSMA-PET scans, there are changes in the staging of prostate cancer with these molecular imaging agents detecting many more lesions than can be seen on traditional imaging. This resultant stage migration calls into question how to interpret the older studies and treatment approaches for oligometastatic prostate cancer. Our modern management of oligometastatic disease usually classifies patients in a category of "low volume, low risk" or "high volume, high risk" disease, based on the well cited CHAARTED, LATITUDE, STAMPEDE and HORRAD clinical trials. With the use of PET-based molecular imaging, it is

increasingly uncertain on how to apply the results of these important clinical trials performed with conventional imaging. By today's standards, there are many more lesions detected due to the higher sensitivity using PSMA-PET imaging. These findings are challenging the historic oligometastatic and risk classification systems.[3]

Molecular imaging has greatly improved the specificity and to a lesser degree, the sensitivity of prostate cancer staging in comparison to conventional imaging with CT, MRI, and bone scans. Beyond staging, PSMA-PET has led to new and improved theragnostics. Here, molecular imaging with PSMA-PET is combined with targeted radionuclide agents such as ^{77}Lu-PSMA-617 to treat late stage, castrate resistant prostate cancer.

Should we be rethinking traditional TNM prostate cancer staging based on PSMA-PET findings? Should M0 be redefined as PSMA-PET and conventional imaging negative and M1 now be reserved for the presence of distant metastasis detected by either conventional imaging or PSMA-PET positivity? Perhaps we may even need a new M0.5 where the only imaging finding is a positive PSMA-PET signal in the pelvis, indicating a local recurrence only following local therapy.

Modern prostate cancer clinical trials have begun to incorporate PSMA-PET for staging and a measure of outcomes. These results will add another dimension to our understanding of how the early detection of metastasis and stage migration impacts trial design and future treatments. There is no doubt that PSMA-PET is a major advance with its superior diagnostic accuracy over standard imaging. While we are hopeful, it remains to be determined if this improved accuracy and earlier detection of prostate cancer recurrence and metastasis will translate to improved outcomes as newer clinical trials incorporate this and other radionuclide imaging technologies.

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References

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