PROSTATE CANCER IN FOCUS

Current Developments in the Management of Prostate Cancer

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Incorporating PSMA PET Imaging Into the Treatment Plan for Newly Diagnosed and Recurrent Prostate Cancer

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H&O What are the advantages of prostate-specific membrane antigen positron emission tomography (PSMA PET) over conventional imaging for prostate cancer?

NS Conventional imaging, which has been the basis for all the phase 3 trials that have led to approvals in prostate cancer over the last 20 years, encompasses computed tomography (CT) with and without contrast, technetium bone scans, and sometimes whole-body magnetic resonance imaging (MRI). These techniques are part of prostate cancer working group guidelines in both the United States and other countries.

Now, conventional techniques are increasingly being replaced throughout the world by PSMA PET, which is just as safe and has better diagnostic accuracy. We still see false-negative and false-positive results, but to a lesser degree than with conventional imaging. Important credit is due the European Association of Nuclear Medicine and the Society of Nuclear Molecular Imaging for reviewing the important trials of PSMA PET and for undertaking educational initiatives to help health care providers better understand the evolving role of PSMA PET.

It is not overly difficult to obtain the equipment needed for PSMA PET; PET cameras have been in use for a long time. Of course, economic accessibility may be a rate-limiting factor. Medical oncologists already have extensive experience with fluorodeoxyglucose (FDG) PET in solid tumors. As for the cost and use case models, PSMA PET will likely enhance the accuracy of staging and thus possibly improve treatment outcomes, thereby increasing efficiencies in comparison with conventional imaging. Thanks to these advances, PSMA PET is being incorporated within various guidelines for the diagnosis and management of prostate cancer.

H&O Which patients with prostate cancer should undergo PSMA PET at diagnosis?

NS A very nice paper that was published in the *Journal of the National Cancer Institute* prioritized the types of patients with newly diagnosed prostate cancer who should be undergoing PSMA PET.[1] PSMA PET is not required for patients who are in grade group 1 or 2 according to the International Society of Urological Pathology system, meaning that they are considered to be at low risk or favorable intermediate risk. Some would argue that PSMA PET could be used in patients who are in grade group 3, meaning that they are considered to be at unfavorable intermediate risk. Recommended prostate-specific antigen (PSA) cutoffs for patients in grade group 3 range from higher than 10 to higher than 20 ng/mL. PSMA PET is strongly recommended for those who are in grade group 4 or 5 because they are considered to have high-risk or highest-risk localized prostate cancer.

We are recognizing that some patients are negative for prostate cancer spread on conventional imaging and positive on PSMA PET, a finding that has resulted in the initiation of numerous clinical trials to further assess these disparate imaging findings and interpretations. Another important area of investigation is differentiation between low-volume results and intermediate- to high-volume results among patients who have positive results on PSMA PET that may not correlate with results on conventional

imaging. Classification of PSMA-positive tumor volume remains ill defined. For example, low volume might refer just to nodal positivity within the pelvis, or it might extend to nodal positivity outside the pelvis. Intermediate volume might refer to nodal positivity in the retroperitoneum, whereas bone metastases in the pubis, pelvis, or axial spine might refer to either intermediate-volume or high-volume disease, depending on the number of lesions. Any nodal positivity within the viscera, lungs, and liver might be considered high-volume disease. Expert consensus is evolving.

H&O How does the use of PSMA PET affect care in the setting of newly diagnosed disease?

NS This is an ongoing area of research and study. If a patient is scheduled for radiation therapy and is negative for nodal spread on conventional imaging but positive for nodal spread within the pelvis or maybe slightly above the pelvis on PSMA PET, how should that affect the radiation field? Perhaps even some soft-tissue findings in the periprostatic space were not appreciated by MRI or CT. This is why ongoing studies are looking at extending the radiation field to treat not just the primary tumor but also the pelvic area or even some extrapelvic areas that are highlighted on PET. These studies are also looking at whether systemic therapy with testosterone suppression and/or androgen receptor pathway inhibition should be implemented for these patients.

Imaging results can also affect the approach of the urologic surgeon in patients who undergo prostatectomy as their primary interventional treatment—specifically, how best to define and optimize the anatomic/surgical borders. We are performing studies to help us learn what the best approach is on the basis of histopathology results, PSA level, MRI findings, digital rectal examination findings, and now the addition of PSMA PET.

H&O How does the use of PSMA PET imaging affect care in the setting of recurrent disease?

NS The setting of biochemical recurrence has been a fascinating area because these are the patients who have already undergone prostatectomy, radiation, prostatectomy with adjuvant radiation, or salvage radiation. Disease is considered recurrent if the PSA level is no longer undetectable in a patient after prostatectomy and if the PSA level is at least 2 points above the nadir in a patient after radiation therapy. In patients with low PSA levels, conventional imaging rarely reveals recurrent disease.

In most cases, approvals for gallium and fluorine products in PSMA PET have been based on biochemical recurrence in patients with negative results on CT and technetium bone scan. The percentages of positive findings on PSMA PET in these approvals were highest among patients with PSA doubling times of less than 12 months and increased proportionally as the PSA level increased from 0.2 to 0.5, from 0.5 to 1, and from 1 to higher than 1 ng/mL. Patients who had a biochemical recurrence after surgery, radiation, or both and had a PSA level between 0.2 and 0.5 ng/mL had positive findings in approximately 30% to 50% of cases. The findings were positive in approximately 50% to 75% of patients who had a PSA level between 0.5 and 1 ng/mL and were higher than 90% in patients who had a PSA level higher than 1 ng/mL. My own experience has been that these percentages are somewhat lower, and this certainly extends to many in community practices who do not have access to the expertise of highly experienced providers of nuclear medicine radiology. There is a fair amount of interobserver variation. That said, patients with a biochemical recurrence can always benefit from PSMA PET because the overwhelming majority will be negative for recurrence on conventional imaging.

How does this affect care? We do not yet have level 1 evidence regarding what to do with this information. What the phase 2 STOMP,[2] ORIOLE,[3] and POPSTAR[4] studies have been able to demonstrate is that radiation treatment to positive areas on the basis of PSMA PET provides the opportunity to delay androgen deprivation therapy (ADT). Multiple phase 3 trials are now addressing the use of various therapeutic strategies in patients who are negative for biochemical recurrence on conventional imaging but positive on PSMA PET, including the ARASTEP trial (NCT0579490). These trials will read out over the next several years.

H&O What should physicians do in the meantime to manage patients who have metastatic disease on PSMA PET but not on conventional imaging?

NS My first response is to say, let us get patients into clinical trials so we can obtain the level 1 evidence we need. Because of the emerging ubiquitous accessibility of PSMA PET in the United States and other countries, health care practitioners are now making decisions in real time that are based on phase 2 studies. I think that providers at tertiary academic medical centers as well as those at community medical centers are asking what to do in this situation. Should they start the patient on ADT? If so, should an androgen receptor pathway inhibitor (ARPI) be used as well?

The phase 3 EMBARK trial demonstrated that for patients who had a biochemical recurrence with a doubling time of less than 9 months, a combination of the ADT leuprolide and the ARPI enzalutamide (Xtandi, Astellas) was better than monotherapy with leuprolide.[5]

Even monotherapy with enzalutamide was better than monotherapy with leuprolide. The results of this study led to a US Food and Drug Administration (FDA) label expansion for enzalutamide in November 2023. This was a very important study that enrolled more than 1000 patients, but it was based on conventional imaging. If we had used PSMA PET in these patients, some of them might have had a small volume of PSMA avidity in 1, 2, or more lymph nodes or perhaps 1 or 2 bone lesions, suggesting a negative to low or intermediate volume. An even smaller percentage might have had a lot of PSMA avidity throughout multiple areas of the bones and lymph nodes and/or viscera.

We do not have level 1 evidence to guide us in what to do, so shared decision making with the patient becomes very important. We also want to bring in a multidisciplinary team through a tumor board to look at all the other factors that affect our decisions: the patient's age, comorbidities, performance status, and preference for systemic therapies.

H&O What studies are being conducted right now with PSMA-directed radiation or radioligand therapies in patients with newly diagnosed disease?

NS The phase 3 VISION trial led to the FDA approval of PSMA radioligand therapy.[6] This landmark study enrolled patients who had metastatic castration-resistant prostate cancer (mCRPC) that had progressed on at least one ARPI and at least one taxane. Patients were randomly assigned to either lutetium Lu 177 PSMA-617 or standard-of-care treatment. The study was successful in terms of demonstrating a benefit in both imaging-based progression-free survival (PFS) and overall survival (OS).

Now, a similar phase 3 study, known as the PSMAfore trial, has achieved its primary endpoint, demonstrating a benefit in radiographic PFS (rPFS).[7] Researchers enrolled patients with taxane-naive mCRPC that had progressed on at least one ARPI; 468 patients were prospectively and randomly assigned to ^{177}Lu-PSMA-617 or another ARPI. In results that were presented at the 2023 European Society for Medical Oncology (ESMO) Congress and later published in the *Lancet*, ^{177}Lu-PSMA-617 was shown to significantly increase rPFS. The study is continuing to see if ^{177}Lu-PSMA-617 also has a positive effect on OS.

Many health care providers have started to use ^{177}Lu-PSMA-617 earlier than in the VISION trial. Numerous studies are also looking at the use of ^{177}Lu-PSMA-617 in patients who have high-risk localized disease and in those who have oligometastatic disease that is still hormone-sensitive. Furthermore, the phase 3 PSMAddition study is looking at the use of ^{177}Lu-PSMA-617 in patients who have metastatic hormone-sensitive prostate cancer (mHSPC).[8] A related phase 3 study, called SPLASH, is looking at a different PSMA-targeted ^{177}Lu-based radioligand therapy called ^{177}Lu-PNT2002 in patients with mCRPC who have not received chemotherapy.[9]

In addition to the ^{177}Lu-PSMA radioligand therapies, a robust amount of clinical trial work is ongoing with other radiopharmaceutical moieties, including actinium, that have ligand backbones to an antibody. These will be examined throughout the continuum of the prostate cancer stages. We may also see trials that evaluate radium Ra 223 dichloride (Xofigo, Bayer) in the population of patients with mHSPC.

Disclosures

Dr Shore has consulted for Accord, Alessa Therapeutics, Amgen, Antev, Arquer Diagnostics, Asieris, Astellas, AstraZeneca, Aura Biosciences, Bayer, BioProtect, Bristol Myers Squibb, Clarity Pharmaceuticals, CG Oncology, Dendreon, Exact Imaging, Ferring, Fize Medical, GlyTherix, Invitae, Janssen, Lantheus, Lilly, MDxHealth, Merck, Minomic, Myriad, Novartis, Photocure, PlatformQ, Pfizer, Preview, Promaxo, Protara, Propella, Sanofi Genzyme, Siemens, Speciality Networks, Sumitomo, Telix, Tolmar, Tutelix, and UroGen.

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