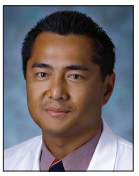
PROSTATE CANCER IN FOCUS

Current Developments in the Management of Prostate Cancer

Section Editor: Andrew J. Armstrong, MD

Management of Oligometastatic Hormone-Sensitive Prostate Cancer



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H&O How is *oligometastatic* defined in the context of hormone-sensitive prostate cancer (HSPC)?

PT We used to make a binary distinction between localized HSPC, which is potentially curable with local therapy, and metastatic HSPC, for which systemic therapy is required. The disease was considered metastatic whether the patient had a single metastatic lesion or hundreds of metastatic lesions. We now realize this disease process is a spectrum, ranging from localized HSPC at one end to widely metastatic HSPC at the other. Hellman and Weichselbaum published a paper in 1995 in which they put forth the concept of oligometastatic disease, an intermediate state between localized disease and widely metastatic disease that might respond to potentially curative local therapies like surgery and radiation.[1]

Various cutoffs have been proposed for the definition of *oligometastatic*, such as fewer than 3, 5, or 7 lesions. The results of the phase 3 STAMPEDE trial have shown us that patients who have newly diagnosed prostate cancer with no more than 3 lesions do the best with local therapy, whereas those who have more than 7 lesions probably do not benefit from local therapy.[2]

H&O Does the diagnosis of oligometastatic HSPC depend on the type of imaging and the sensitivity of detection?

PT We have seen that the number of lesions detected depends on the detection method used. A patient who has 3 lesions on a conventional imaging test, such as computed tomography (CT), magnetic resonance imaging (MRI), or a bone scan, is likely to have a larger number of lesions on advanced molecular imaging, such as prostate-specific membrane antigen (PSMA) positron emission tomography (PET). This stage migration is sometimes referred to as the Will Rogers phenomenon. We need to be aware of stage migration as we continue to study oligometastatic disease and re-define these clinical cutoffs.

We do need to have specific cutoffs for numbers of metastases to guide our research and clinical practice. But even more important than the precise number of lesions is the underlying biology of the individual patient's cancer, which we hope will let us know which patients need systemic therapy in addition to local therapy. Our group took part in a study recently published in *European Urology* that compared, for the first time, patients with a diagnosis of oligometastatic HSPC based on conventional imaging vs those with a diagnosis based on advanced molecular imaging.[3] The 295 patients in the study had metachronous or recurrent disease rather than synchronous or de novo disease. We found clinical and biological differences between the patient groups depending on how oligometastasis was detected; patients in the conventional imaging group had a higher prostate-specific antigen (PSA) level at the time of metastasis, were more likely to have *TP53* and other adverse mutations in their primary tumor, and had a worse overall survival (OS) in comparison with patients whose diagnosis of oligometastasis was based on advanced

molecular imaging. This finding tells us that these are probably 2 different types of biology that we are picking up, even though we are using the same cutoff of 3 or 5 metastatic lesions.

H&O What is the current standard of care for men with synchronous or de novo oligometastatic HSPC?

PT Several trials have established the current standard of care for patients with synchronous or de novo disease that is low-volume. The first component is systemic therapy, which consists of intensified hormone therapy with a luteinizing hormone-releasing hormone (LHRH) agonist or antagonist plus an androgen receptor pathway inhibitor such as enzalutamide (Xtandi, Astellas), apalutamide (Erleada, Janssen), or abiraterone. The evidence for enzalutamide plus androgen deprivation therapy (ADT) is based on the ENZAMET and ARCHES studies.[4,5] The TITAN study established that apalutamide plus ADT improves outcomes in those patients.[6] In addition, the phase 3 STAMPEDE trial has shown that numerous agents, especially abiraterone, work best in combination with ADT in patients with de novo low-volume or oligometastatic HSPC.[7]

The second component is localized therapy directed at the primary tumors. We have level 1 evidence from STAMPEDE arm H and the phase 3 PEACE trial showing that therapy directed at the primary prostate tumors is helpful in patients who have metastatic disease, especially those with low-volume or oligometastatic disease. In STAMPEDE arm H, the addition of radiation therapy to ADT improved OS at 3 years, and most recently at 5 years.[8,9] The phase 3 PEACE-1 trial, which included an arm that received primary prostate radiation, also demonstrated benefits from radiation that included increased time to castration resistance.[10] The addition of radiation did not appear to increase the risk of severe local side effects.

Should there be a third component, in which therapy is directed specifically at the metastases? This question has not yet been definitively addressed by any trials, but several ongoing trials are beginning to look at it, including the phase 3 STAMPEDE2 (NCT06320067) and PLATON (NCT03784755) trial. In addition, the phase 2 TERPS trial here at the University of Maryland (NCT05223803) is planning to enroll 122 patients with de novo low-volume or oligometastatic HSPC and randomize them to the standard of care, meaning best systemic therapy and primary prostate radiation, plus or minus stereotactic ablative radiation (SABR) metastasis-directed therapy. When the results of these trials become available, in as soon as 4 to 5 years, they should add to the body of evidence establishing whether metastasis-directed therapy is beneficial to these patients with de novo disease.

H&O What is the current standard of care for men with metachronous or recurrent oligometastatic HSPC?

PT Patients with metachronous or recurrent disease have already received surgery, radiation, or a combination of both. In most of these cases, recurrence is detected by an elevated PSA test result. From the results of retrospective series and clinical trials, we know that upwards of two-thirds or three-quarters of patients in whom metastatic disease develops after localized disease, based on biochemical recurrence, usually have low-volume or oligometastatic disease rather than polymetastatic or widely metastatic disease.

> We and others have contributed to the idea that certain genomic factors may correlate with worse outcome in the metachronous or recurrent oligometastatic setting.

We have good data from Sutera and colleagues and Kyriakopoulos and colleagues showing that among patients with low-volume metastatic HSPC, those with recurrent disease have better clinical outcomes than those with de novo disease.[11,12] The disease biology is believed to be more aggressive among patients with de novo disease. A lot of heterogeneity is seen among patients with recurrent disease, and because of its more indolent biology, it is possible that a small minority of patients may not even need to be treated. As an example, if patients have just 1 or 2 small pelvic lymph nodes detected by PSMA and they are already in their late 70s or early 80s, the disease may never catch up with them.

On the other end of the spectrum are patients who have aggressive disease, with rapid PSA doubling times, a history of high Gleason scores, and certain high-risk mutations. We and others have contributed to the idea

that certain genomic factors may correlate with worse outcome in the metachronous or recurrent oligometastatic setting, including mutations in *TP53*, *BRCA1/2*, *ATM*, and *RB*. Acceptable standards of care for these patients range from an active surveillance approach to intensified hormone therapy, which was discussed earlier. As a radiation oncologist, I am especially interested in the question of whether the disease of these patients is amenable to local therapies, such as SABR metastasis-directed therapy.

We have more prospective data in the recurrent setting than in the de novo setting, with at least 3 trials looking at recurrent oligometastatic HSPC. In the phase 2 STOMP trial, by Ost and colleagues, 62 patients with 1 to 3 metastases on choline PET were randomized to observation vs SABR metastasis-directed therapy.[13] In the phase 2 ORIOLE trial, from our group, we enrolled 54 patients with 1 to 3 metastases on conventional imaging and randomly assigned them to observation vs SABR metastasis-directed therapy.[14] In an update and combined analysis of the 2 studies that we published in 2022, we were able to establish a persistent signal of benefit with the use of metastasis-directed therapy.[15] This is excellent news because it means that SABR metastasis-directed therapy has the potential to allow either intermittent ADT or longer periods off ADT. The analysis also included molecular profiling that suggested a larger benefit of SABR metastasis-directed therapy in patients with a high-risk mutation. Finally, the phase 2 EXTEND study suggested that the addition of SABR metastasis-directed therapy to hormone therapy—either standard or intensified—improved both progression-free survival (PFS) and eugonadal PFS, defined as the time from achieving a testosterone level of 150 ng/dL or less until progression.[16]

H&O What would you say is the current role of SABR metastasis-directed therapy according to these results?

PT I know that some practitioners are using it already, but we do not yet have level 1 evidence for SABR metastasis-directed therapy, so it really should be used within the confines of a clinical trial. Fortunately, multiple phase 3 clinical trials are looking at this question now, and we hope to see definitive results soon.

H&O What are the options for patients who need more-intensive treatment?

PT We know that certain patients do poorly, such as those with high-risk mutations. A recently opened phase 2 trial, called KNIGHTS, is enrolling patients with high-risk metachronous oligometastatic HSPC to see whether adding the poly(ADP-ribose) polymerase inhibitor niraparib plus abiraterone acetate (Akeega, Janssen Biotech) to SABR and ADT can improve outcomes (NCT06212583). I believe this is the only integral biomarker-driven trial in this space.

H&O Are the results of SABR metastasis-directed therapy different in the castration-resistant setting?

PT The phase 2 ARTO trial, from Italy, randomly assigned patients with oligometastatic castration-resistant prostate cancer to standard care with abiraterone plus or minus SABR metastasis-directed therapy. Early results on 157 patients have shown a significant improvement in PFS with the addition of SABR to treatment, although it is too early to say anything about OS.[17] We do know that when patients have metastatic disease, castration resistance does not occur in every single metastatic lesion. Resistance usually occurs in a few clones in a limited number of metastatic lesions, which disseminate over time and contribute to broader resistance. The theory is that if you can pick off these resistant clones before they expand to the rest of the body, you might be able to improve control with whatever treatment you are administering.

Disclosures

Dr Tran has served in a consulting/advisory role to Natsar Pharmaceuticals, Astellas Pharma, RefleXion Medical, Bayer Health, Regeneron, Dendreon, Noxopharm, Janssen, Myovant Sciences, AstraZeneca, and Lantheus; has received research funding from Astellas Pharma, RefleXion Medical, and Bayer Health; and holds a patent with Natsar Pharmaceuticals (Compounds and methods of use in ablative radiotherapy, patent filed 3/9/2012. PCT/US2012/028475. PCT/WO/2012/122471), licensed with royalties to Natsar Pharmaceuticals. He has received funding from the NIH/NCI (U01CA212007, U01CA231776, 1R01CA271540, and U54CA273956), the Movember Foundation, the Distinguished Gentleman's Ride, the Prostate Cancer Foundation, the Department of Defense (W81XWH-21-1-0296), and an anonymous donor.

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