PROSTATE CANCER IN FOCUS

Current Developments in the Management of Prostate Cancer

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New Staging Systems in Nonmetastatic Prostate Cancer

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H&O How is prognosis typically estimated in nonmetastatic prostate cancer?

FF We typically estimate prognosis with a variety of tools, including the Gleason score; levels of prostate-specific antigen in the blood; and tumor staging based on a physical examination, which in some cases is augmented with magnetic resonance imaging or ultrasound. The clinical staging system from the National Comprehensive Cancer Network (NCCN), which has been the conventional staging system for more than 2 decades, incorporates these tools and has been validated multiple times—its use is supported by level-1 evidence. Most clinicians use the NCCN system because it is fast, convenient, and accessible, and has been around for a long time.

H&O What newer staging systems are in use in nonmetastatic prostate cancer?

FF Newer clinical staging systems for use in patients with nonmetastatic prostate cancer are STAR-CAP, CAPRA, and the Memorial Sloan Kettering Cancer Center nomogram. All 3 of these systems have been validated with level-3 evidence (as defined in 2023 NCCN Guidelines) and include additional clinical features to more precisely estimate the rate of certain endpoints. The STAR-CAP tool is trained for prostate cancer–specific mortality at 5 and 10 years, the CAPRA tool is trained for biochemical recurrence, and the Memorial Sloan Kettering Cancer Center nomogram is trained for both prostate cancer–specific mortality and biochemical recurrence.

Novel approaches to risk stratification are also emerging. The 2023 NCCN Guidelines include 3 options for gene expression tools: Decipher Biopsy from GenomeDx, Prolaris Biopsy from Myriad Genetics, and the Genomic Prostate Score test (formerly Oncotype DX GPS) from mdxhealth. The use of Decipher, which looks at the RNA expression of 22 genes and estimates the rate of distant metastasis at 5 years after treatment, is supported by level-1 evidence, including research from Tran, myself, and colleagues at NRG Oncology that was published in *JAMA Oncology* in 2021. The use of Prolaris, which looks at the expression of multiple genes involved in cell proliferation, is supported by level-3 evidence from Cuzick and colleagues. Finally, the use of the Genomic Prostate Score test, which was trained against the endpoint of adverse pathology on subsequent surgery, is supported by level-3 evidence from Klein and colleagues. Gene expression tools are increasing in popularity, in part because they are increasingly likely to be covered by insurance programs, including Medicare.

The most recent advance in risk stratification is the use of artificial intelligence to analyze digitized pathology images. The ArteraAI Prostate Test estimates the rates of biochemical recurrence, distant metastases, and dying of prostate cancer based on information from several clinical factors plus analysis of a single hematoxylin and eosin (H&E) pathology slide. Although this is the newest approach, it is supported by level-1 evidence based on a study of 5654 patients with Esteva as the first author. This

study showed that the AI models were 9.2% to 14.6% better than the NCCN system at predicting outcomes among various endpoints. I was an investigator in this study and have been an advisor to Artera, so there is bias, but I am excited about this approach. The 2023 NCCN Guidelines list 3 risk stratification approaches as having level-1 evidence: the NCCN system, ArteraAI, and Decipher. The fact that ArteraAI and Decipher have both outperformed the NCCN system in randomized trials makes them especially appealing options. I also like the fact that when the use of AI classifiers becomes widespread, the results will be instantaneous. I love the genomic classifiers, but results take 2 or 3 weeks to come back, which creates anxiety for patients.

> I expect that novel risk stratification will soon be the norm in the vast majority of clinical trials that are launched.

H&O How do you incorporate clinical staging or risk systems into your practice for patients with localized prostate cancer?

FF Risk stratification is important in a variety of clinical decisions. One of the more important decisions is whether a patient with low-risk or favorable intermediate-risk prostate cancer should receive active surveillance or some form of active treatment, such as surgery or radiation therapy. Active surveillance is safe in most patients with low-risk prostate cancer, but a subset of those patients still experience progression. My approach is to recommend active surveillance for most of my low-risk patients, but if my patients are uncomfortable with that approach, I will order genomic classification. If the genomic risk score is high, I am more likely to lean toward recommending surgery or radiation.

Another use of risk stratification is in the context of patients who plan to pursue radiation as a treatment approach. For these patients, understanding the later risk of metastatic disease has the potential to help us in tailoring treatments. For example, if a patient with intermediate-risk prostate cancer is being treated with up-front radiation, the addition of short-course hormone therapy has the potential to be beneficial. The traditional approach is to classify patients as having either favorable or unfavorable intermediate-risk prostate cancer based on the NCCN criteria. We tend to use radiation alone in patients with favorable intermediate-risk prostate cancer and we tend to use radiation plus short-course androgen deprivation therapy (ADT) in patients with unfavorable intermediate-risk prostate cancer. The addition of genomic classifiers can give us a better estimate of the rate of metastatic disease. For example, some men with unfavorable intermediate-risk prostate cancer still have a low genomic risk of metastasis and can safely skip ADT.

I have extensive experience with Decipher, having taken part in a study published in *JAMA Oncology* in 2021 in which we validated its use based on specimens from the phase 3 RTOG 9601 trial. RTOG 9601 enrolled patients who experienced a recurrence of prostate cancer after surgery, and found that the addition of ADT to radiation improved outcomes. What our analysis found is that patients who had a lower Decipher score were far less likely to benefit from the addition of ADT to radiation. One caveat to our study is that it did not determine specific statistical thresholds to use when making treatment decisions, but Decipher does give us an additional decision-making tool. The hope is that either existing tools will prove to be predictive in the postoperative setting or new tools will be developed.

H&O What ongoing studies are looking at staging systems in localized prostate cancer?

FF The ongoing, national phase 3 GUIDANCE trial (also known as NRG-GU010) is using the Decipher risk score to determine whether patients with unfavorable intermediate-risk prostate cancer should receive ADT (NCT05050084). Patients with a low Decipher score are randomly assigned to radiation alone vs radiation plus 6 months of ADT, whereas those with a high Decipher risk score are randomly assigned to radiation and 6 months of ADT or to the same treatment plus 6 months of darolutamide (Nubeqa, Bayer), which is a next-generation antiandrogen therapy. Clearly, there is a desire to use additional tools besides NCCN risk staging to be able to better tailor therapy, with the general concept being that the more the aggressive the cancer, the more we should intensify therapy, and the less aggressive the cancer, the more we can de-intensify therapy. Either way, the key is having a prognostic tool such as Decipher.

Another ongoing trial is PREDICT-RT, also known as NRG-GU009 (NCT04513717). In this study, patients with high-risk prostate cancer are assigned to a randomized trial of less-intensive treatment if they have a lower Decipher score, and a randomized trial of more-intensive

treatment if they have a higher Decipher score. This is a well-designed study, and I expect that novel risk stratification will soon be the norm in the vast majority of clinical trials that are launched.

H&O Can any of these tools predict response to treatment?

FF One of the exciting aspects of AI tools is that they can predict response to treatment in addition to determining prognosis. Speaking at the at the 2022 American Society of Clinical Oncology (ASCO) Genitourinary Cancers Symposium, Dr Daniel Spratt reported on the use of AI to determine which patients with localized prostate cancer would benefit from ADT. This study examined data on 1719 patients with localized prostate cancer, primarily intermediate-risk, from the phase 3 NRG/RTOG 9408 trial who were randomly assigned to either radiation alone or radiation plus ADT. The results showed that patients who had biomarker-positive disease using AI were far more likely to benefit from the addition of ADT to radiotherapy, as measured by the subsequent development of distant metastases. That is an exciting finding because it gives us a tool to tell us whether a specific patient will benefit from ADT or not—a tool that goes beyond just telling us whether the risk of recurrence was higher or lower. We already have prognostic tools for many decision points, but we also need predictive tools.

Disclosures

Dr Feng has served as an advisor to Artera; has received research support from Artera and Decipher; and has served as a consultant for Janssen, Bayer, Novartis, Genentech, Myovant, Sanofi, Roivant, Myovant, BMS, Astellas, Blue Earth Diagnostics, and Tempus.

Suggested Readings

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