Management of Patients With Nonmetastatic Prostate Cancer

Presented by Julio M. Pow-Sang, MD

ABSTRACT

Localized prostate cancer is a heterogeneous disease. However, some diagnostic features are helpful in categorizing patients into risk groups for adverse outcomes, such as pathology, imaging, and genetic profiling. Risk-specific management options, including active surveillance, can be tailored to individual patients based on their risk profile. Clinicians should discuss the risks and benefits of each of these options with patients for informed decision-making.

Although localized prostate cancer is a heterogeneous disease, certain diagnostic features—pathology, imaging, and genetic profiling—can be helpful in categorizing patients into risk groups for adverse outcomes. At the NCCN 2022 Annual Conference, Julio M. Pow-Sang, MD, Chair, Department of Genitourinary Oncology, Moffitt Cancer Center, discussed standard tools for risk stratification, including prostate-specific antigen (PSA), Gleason score, and T stage, and described newer modalities, such as MRI, prostate-specific membrane antigen (PSMA) PET/CT, genomic markers, and genetic testing. Dr. Pow-Sang also shared various management options for nonmetastatic prostate cancer, including active surveillance/observation, radiation therapy (RT), and surgery.

Prostate Cancer Statistics

Prostate cancer is the most common cancer and the second-leading cause of cancer mortality in American men.1 Although prostate cancer is more common in Black men, its incidence and mortality have steadily decreased over the past 30 years. Furthermore, it is a disease of aging and becomes more prevalent after age 50 years, said Dr. Pow-Sang. He noted that the prevalence increases between the ages of 60 and 75 years before decreasing over time. Prostate cancer-specific mortality, conversely, continues to increase with age and rises significantly after age 85 years.1

Nearly three-quarters of patients present with localized disease (74%), confined to the primary site, whereas 13% of patients present with regional disease, which has spread to regional lymph nodes at diagnosis. Approximately 7% of patients who present have disease that has metastasized at diagnosis (6% of all cases are unstaged).1

Risk Stratification

As Dr. Pow-Sang explained, localized prostate cancer is a heterogeneous disease. Although some cancers grow slowly or very slowly, staying dormant for decades, other cancers grow slowly and progress over years. Additionally, a small percentage of cancers present as aggressive, progress rapidly, and fail to respond to local treatment modalities.

According to Dr. Pow-Sang, the purpose of risk stratification is twofold: to determine the likelihood of (1) prostate cancer remaining confined versus spreading to the lymph nodes, and (2) disease progression or metastasis after treatment. “It’s important to understand that risk stratification is prognostic but not predictive of benefit to any specific treatment,” he said.

Dr. Pow-Sang listed the following traditional tools used for risk stratification: digital rectal examination (DRE); Gleason score (6–10) or Grade Group (1–5), with percentage of total positive cores and percentage of cancer per core; PSA level; PSA density; and life expectancy. Newer tools to improve risk stratification include imaging, gene expression biomarkers, and germline testing. However, to simplify the process, patients are divided into low-risk (including very low risk), intermediate-risk (including favorable and unfavorable), high-risk, and very high-risk groups, he said (Figure 1).

Prostate Cancer Diagnosis

According to the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Prostate Cancer, initial workup involves a physical examination and a DRE to confirm clinical stage. PSA level should be collected at time of diagnosis and used to calculate PSA density and doubling time. It’s also important to obtain and review
diagnostic prostate biopsies, and the physician should determine patient life expectancy, which can influence the decision to place the patient on active surveillance or even observation. Recently, a recommendation was added to inquire about the probability of high-risk germline mutations, which are associated with poor outcomes in those with newly diagnosed prostate cancer. Finally, it is important to obtain a family history of prostate cancer.

Dr. Pow-Sang admitted that the Gleason grading system, which is used to help evaluate the prognosis of patients with prostate cancer using samples from a prostate biopsy, was initially difficult for many patients and providers to understand. The International Society of Urological Pathology now categorizes patients into 1 of 5 groups based on Gleason score (Figure 2). Pathology review also considers the number of cores involved of the total cores obtained from biopsy, and the percentage of cancer in each core.

**Imaging in Staging and Risk Stratification**

More recently, multiparametric prostate MRI and PSMA PET/CT scan have improved risk stratification for patients who present with newly diagnosed prostate cancer. Multiparametric prostate MRI is becoming an established procedure to determine the need for biopsy and to improve the detection of clinically significant cancer. It provides an accurate measurement to determine prostate size and to calculate PSA density.

When there is a visible lesion, said Dr. Pow-Sang, the radiologist will determine the PI-RADS (Prostate Imaging Reporting and Data System) rating from 1 to 5. A lesion with a PI-RADS rating of 4 or 5 in combination with a positive biopsy Grade Group $\geq 2$ helps to determine the location and extent of significant cancer.

Another more recent advance in risk stratification is going beyond bone and soft tissue imaging to assess for metastases. As Dr. Pow-Sang explained, PSMA PET/CT allows for a higher sensitivity and specificity beyond what a bone scan or pelvic CT scan can yield. The NCCN Guidelines consider conventional imaging a prerequisite to PSMA-PET but note that this modality can serve as “an equally effective, if not a more effective, frontline imaging tool for these patients.”

**Genetic Testing**

According to Dr. Pow-Sang, genetic testing is complicated, and several unanswered questions remain. However, the NCCN Guidelines thoroughly outline many of the challenges associated with genetic testing. The guidelines recommend inquiring about family and personal histories of cancer, as well as known germline variants at the time of initial diagnosis. Germline testing should also be
considered when it is likely to impact treatment and clinical trial options, management of risk of other cancers, and/or potential risk of cancer in family members. If these criteria are met, germline multigene testing should include at least BRCA1, BRCA2, ATM, PALB2, CHEK2, MLH1, MSH2, MSH6, and PMS2.

Posttest genetic counseling is strongly recommended if a germline mutation is identified, he said, because there are many potential downstream effects. Cascade testing for relatives, for example, is critical to determine the risk of familial cancers in all relatives.

**Active Surveillance and Observation**

With respect to treatment, active surveillance involves actively monitoring patients diagnosed with low-risk or favorable intermediate-risk prostate cancer, with the expectation to intervene with curative intent upon disease progression. Per the NCCN Guidelines, life expectancy is a key determinant for the treatment options of observation, active surveillance, and definitive treatment. Active surveillance is preferred for patients with very low risk prostate cancer and a life expectancy ≥10 years, whereas observation is preferred for those with a life expectancy <10 years and very low risk disease. Patients with favorable intermediate-risk prostate cancer and a life expectancy >10 years may also consider active surveillance.

Observation involves monitoring a patient with physical examinations once a year but without further testing, such as MRI or rebiopsies, and only intervening if the patient becomes symptomatic. The protocol for active surveillance involves PSA testing no more than 6 months, DRE no more than every 12 months, and repeat prostate biopsy no more than every 12 months.

"Generally, the field is moving toward doing a prostate biopsy every 2 to 3 years provided that yearly MRI scans and PSA levels remain stable or show no changes," said Dr. Pow-Sang.

**Radiation Therapy**

According to Dr. Pow-Sang, RT has gone through a revolution in technology with linear accelerators, improved computers, and an improved understanding of the physiologic interaction between radiation and cancer. There are 3 types of external-beam RTs: moderate hypofractionation, conventional fractionation, and ultrahypofractionation.

Moderate hypofractionation, which is the preferred modality, involves giving moderate amounts of doses for approximately 4 to 5 weeks. Conventional fractionation involves 37 to 45 treatments with lower doses. A more recent development in the past decade, ultrahypofractionation delivers RT in 5 or 7 treatments during a period of 1 to 2 weeks.

Another treatment modality is brachytherapy or implant. There are 2 main types of implants: (1) permanent implants of low-dose radiation using iodine, palladium, or cesium, and (2) a temporary implant of high-dose RT using
iridium-192. Finally, a combination of external RT with either permanent implant with low-dose radiation or temporary implant with temporary high-dose radiation is an option.

**Surgery**

With respect to surgery, Dr. Pow-Sang noted that radical prostatectomy also underwent significant technical improvement. Understanding of how extensive surgery must be has improved, and most surgeries are now robotically assisted using laparoscopy, he said. Radical prostatectomy is appropriate for patients with a life expectancy of ≥10 years with clinically localized prostate cancer that can be completely excised surgically.

A pelvic lymph node dissection should be performed at prostatectomy in those with unfavorable intermediate-risk, high-risk, or very high-risk disease. Extended pelvic lymph node dissection provides more complete staging and may cure some patients with microscopic metastases.

**Disclosures:** Dr. Pow-Sang has disclosed serving as a scientific advisor for Lantheus.

**Correspondence:** Julio M. Pow-Sang, MD, Department of Genitourinary Oncology, Moffitt Cancer Center, 12902 Magnolia Drive, Tampa, FL 33612. Email: julio.powsang@moffitt.org

**References**