NCCN Guidelines Updates: Management of Prostate Cancer

Presented by James L. Mohler, MD, and Emmanuel S. Antonarakis, MD

ABSTRACT

Updates to the NCCN Guidelines for Prostate Cancer include further refinements in taking a family history, new recommendations for germline and somatic testing, use of androgen receptor blockers for nonmetastatic castration-resistant prostate cancer, advice regarding intermittent versus continuous androgen deprivation therapy, and consideration of whether to treat the primary tumor in men diagnosed with de novo metastatic prostate cancer.

“The additional refinements in the 2019 NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Prostate Cancer on what constitutes a family history of prostate cancer will help practitioners know what to inquire about,” said James L. Mohler, MD, Associate Director for Translational Research, Chief of Inter-Institutional Academics, and Professor of Oncology, Roswell Park Comprehensive Cancer Center. “We are advising that a more thorough history be taken for family members found to have genomic abnormalities, especially for homologous repair deficiency [HRD] genes [Figure 1]. We have refined the definition of what constitutes a first-degree relative, advised more careful ascertainment of Ashkenazi Jewish ancestry, and refined the definition of hereditary risk.”

Germline variants known to be associated with increased incidence and/or aggressiveness of prostate cancer include MSH2, MSH6, and MLH1 (Lynch syndrome) and BRCA1, BRCA2, ATM, PALB2, and CHEK2 (homologous recombination genes). The new guidelines call for germline testing for all of these using next-generation sequencing (NGS). Additional genes should be tested depending on clinical context. Some of these may not be actionable but are of value in family counseling (eg, HOXB13).

Another important feature in the 2019 version of the NCCN Guidelines for Prostate Cancer is a distinction between intraductal and ductal carcinoma. Although both can occur within the same biopsy and there can be overlap, a higher incidence of germline mutations may be found in intraductal carcinoma, which has treatment implications.

“Four different studies have found an association between DNA repair genes and intraductal carcinoma,” Dr. Mohler said. “Ongoing studies are prospectively testing this potential association.”

The 2019 guidelines recommend germline testing for all patients with intraductal carcinoma and state that germline testing should be “considered” for ductal carcinoma based on clinical features (Figure 2). “We have included when to recommend germline testing according to risk category and family history for all risk groups. The frequency of germline mutations represents a rapidly evolving knowledge base,” he said. “Some studies show that even as you capture patients at more advanced stages of prostate cancer, the frequency remains relatively low but targeted therapy may be quite beneficial.”

NGS for a full gene panel costs approximately $3,500 per patient. Targeted sequencing of specific genes can be performed at a reduced cost, and the cost to the patient depends on insurance coverage and patient co-pays. “A danger of limiting sequencing to save costs is that genes that can be targeted to affect the course of disease may be missed,” Dr. Mohler said.

Intermediate Risk: Favorable Versus Unfavorable

“The intermediate-risk group can be controversial. The current guidelines stratify intermediate-risk patients according to favorable versus unfavorable. Cancers in these 2 groups of patients behave differently,” Dr. Mohler said.

Favorable intermediate-risk patients have 1 intermediate risk factor, Grade Group 1 or 2 cancer, and <50% of cores positive. Unfavorable intermediate-risk patients have 2 or 3 intermediate risk factors, and/or Grade Group 3 prostate cancer, and/or ≥50% of biopsy cores positive.
We need to apply caution here. We believe active surveillance should be offered to men with favorable intermediate-risk prostate cancer, but this needs to be considered carefully,” he told the audience.

Active surveillance in this setting may include a molecular-based test, 3P MRI, restaging prostate biopsy, surveillance 3P MRI, surveillance prostate biopsies, some combination thereof, or prospective clinical trials.1

**Androgen Deprivation Therapy**

“I am an advocate of using less androgen deprivation therapy [ADT]. We should not be using ADT in NCCN low-risk patients. When used properly, ADT is beneficial. When used as neoadjuvant therapy along with radiation, ADT reduces the size of the target so that radiation can be delivered with greater oncologic efficacy and fewer side effects. Adjuvant ADT also is effective in high-risk prostate cancer,” he stated. “According to recent evidence, we can shorten the course of ADT from 2 to 3 years to 1.5 years. The oncologic outcomes seem to be similar.”

Patients with positive lymph nodes (pN1) during radical prostatectomy have been treated with ADT based on a trial published in 2006 showing significantly improved overall survival (OS) and recurrence-free survival at 12 years of follow-up with immediate ADT versus delayed ADT (P<.0001).2 However, subsequent trials failed to replicate these results, he said.

“Use caution when subjecting men with node-positive prostate cancer to lifelong ADT,” Dr. Mohler advised.

The NCCN Prostate Cancer Panel included a statement in the latest version of the guidelines to the effect that it is uncertain whether radiation of regional nodes improves outcomes, and nodal treatment should be performed in the context of a clinical trial.

**Intermittent Versus Continuous ADT**

“Always think about intermittent ADT,” Dr. Mohler continued. “Several studies have compared these 2 approaches. The best analysis found no survival benefit for continuous versus intermittent ADT. No subgroup favors continuous ADT, and quality of life [QoL] is better during the off cycle,” he stated.

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**Figure 1.** Factors used to determine positive family history in 2019. Abbreviation: CaP, cancer of the prostate.

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**Figure 2.** NCCN Guidelines for Prostate Cancer recommend germline testing for some patients with prostate cancer.
A large meta-analysis of 6 randomized trials comprised of 2,996 men found similar OS for intermittent versus continuous ADT, with improved QoL associated with intermittent ADT.3

SWOG 9346 found that continuous ADT was associated with approximately a 6-month advantage in survival versus intermittent ADT in metastatic hormone-sensitive prostate cancer but with a worse QoL.4 At a median follow-up of 9.8 years, median OS 5.1 years in the intermittent therapy group.

“The panel softened our recommendations some time ago to consider intermittent ADT in all men with nonmetastatic prostate cancer and also to consider it in metastatic disease. I believe intermittent ADT should be considered in everyone. ADT can be personalized according to end-of-induction prostate-specific antigen [PSA] levels,” Dr. Mohler said.

New Controversies
Treatment of the primary tumor in patients diagnosed with low-volume metastatic disease is controversial, with advocates on both sides of the issue.

The recent HORRAD randomized trial of >500 men diagnosed with low-volume metastatic disease to the bone found no difference in survival whether men on ADT had radiation to the primary tumor or not.5

Arm H of the STAMPEDE trial basically replicated those results in men with newly diagnosed prostate cancer; 40% had a low metastatic burden, 56% had a high metastatic burden, and 6% had unknown disease burden. Overall, no benefit was found, but a prespecified subset analysis suggested benefit in the low metastatic volume group. “This is still controversial. It behooves us to find out whether low-volume [metastatic] disease benefits from irradiation of the primary tumor,” Dr. Mohler told the audience. “Ongoing clinical trials should give us the answer.”

Several randomized controlled trials are looking at patients with low-volume disease on ADT treated with either surgery or radiation versus ADT alone (eg, SWOG 1802, g-RAMPP, PEACE1).

Nonmetastatic Castration-Resistant Disease
What about ADT in men with increasing PSA and no evidence of metastasis? New to the NCCN Guidelines for Prostate Cancer in 2019 is a recommendation for second-generation antiandrogen therapy with either enzalutamide or apalutamide in patients already on ADT. It is now a category 1 recommendation to give enzalutamide or apalutamide to men with nonmetastatic castration-resistant prostate cancer (CRPC) and a PSA doubling time of ≤10 months.

More recently, the ARAMIS trial found that darolutamide, another second-generation antiandrogen, delayed the emergence of metastases.7 Metastasis-free survival was improved from 18.4 months with placebo to 40.4 months with darolutamide (P<.001). However, darolutamide is not yet included in the guidelines because it lacks FDA approval.

“Studies have shown a delay in the time to development of metastatic disease, but as yet there is no OS benefit. The committee felt that being free of metastasis was an important QoL issue,” Dr. Mohler said.

Financial Considerations
“Although it is considered an advance to delay the time to metastasis, these new agents are quite expensive. Use of these oral drugs will add another $400,000 to the cost of treatment. New agents have extended survival from the time of bone metastases from 3 to 5 years. If one assumes each man can take each agent and attain the survival benefit gained in the FDA registration trials, total medication costs will have increased to approximately $1 million. We need to consider cost and its resulting financial distress,” he said. “The financial burden of cancer has a greater impact on survivors of prostate cancer than any of the other 7 common cancers. We need to be particularly concerned about our patients with advanced prostate cancer.”

Another concern Dr. Mohler raised is that new PET imaging will identify more men with micrometastases. This could cause “stage migration,” requiring treatment for longer periods. However, this earlier detection and resultant treatment may not change outcome.

Integrating Genomic Testing Into Practice
Results of somatic genomic testing can inform treatment in men with prostate cancer, explained Emmanuel S. Antonarakis, MD, Associate Professor of Oncology and Urology, The Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, and Director of Prostate Cancer Medical Oncology Research.

Dr. Antonarakis went into greater detail regarding genomic testing. DNA repair mutations are found in prostate cancer—both single-strand repair (eg, mismatch repair [MMR]) and double-strand repair mutations (eg, HRD), of which alterations in BRCA1/2 are the most common.

The prevalence of these mutations differs according to localized versus metastatic disease.8 In primary tumors, biallelic DNA repair gene mutations are found in approximately 8% to 10%, whereas they occur in about 20% to 25% of metastatic CRPC, he explained.

A recent paper analyzed DNA repair defects in ductal prostate cancer and found that 49% of patients had somatic DNA repair gene mismatches that were actionable (14% MMR, 31% HRD).9 The 2019 version of the
NCCN Guidelines recommends testing for HRD and for microsatellite instability (MSI) or MMR deficiencies in all patients with metastatic prostate cancer. An increased prevalence of these mutations might be found in advanced ductal prostate cancers.

**Therapeutic Implications of Somatic Genomics**

MMR gene deficiency tumors occur in approximately 2% to 4% of patients with metastatic prostate cancer. Pembrolizumab was approved by the FDA 2 years ago for all forms of MSI-high solid tumors, including MMR-deficient advanced prostate cancers. Pembrolizumab is included in the 2019 NCCN Guidelines as a category 2B recommendation for second-line metastatic CRPC therapy and as subsequent treatment. Pembrolizumab is administered in a flat dose of 200 mg intravenously every 3 weeks.

“There are no prospective randomized data yet for first-line metastatic CRPC treatment with pembrolizumab in MSI-high tumors, but I would argue that it could be a first-line therapy in certain settings,” Dr. Antonarakis said. HRD mutations are present in 20% to 25% of patients with metastatic CRPC. If germline or somatic mutation testing reveals the presence of HRD mutations, investigational PARP inhibitors have been to be found effective in patients with BRCA1/2. However, PARP inhibitors are not FDA-approved at this time for prostate cancer.

Both olaparib and rucaparib can be considered as investigational therapy for patients with HRD mutations, but only within the context of a clinical trial, according to the updated NCCN Guidelines for Prostate Cancer.

**Disclosures:** Dr. Mohler has disclosed that he has no financial interests, arrangements, affiliations, or commercial interests with the manufacturers of any products discussed in this article or their competitors. Dr. Antonarakis has disclosed that he serves as a consultant for Amgen Inc., Astellas Pharma US, Inc., AstraZeneca Pharmaceuticals LP, Clovis Oncology, Dendreon Corporation, ESSA, GlaxoSmithKline, Janssen Pharmaceutica, Medivation, Inc., Merck & Co., Inc., and sanofi-aventis U.S.; that he has received grant/research support from AstraZeneca Pharmaceuticals LP, Bristol-Myers Squibb Company, Celgene Corporation, Clovis Oncology, Dendreon Corporation, Genentech, Inc., Janssen Pharmaceutica, Johnson & Johnson, Merck & Co., Inc., Novartis Pharmaceuticals Corporation, sanofi-aventis U.S., and Tokai; and that he has received royalty income from Qiagen.

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**References**