NCCN Guidelines® Insights

Prostate Cancer, Version 3.2012

Featured Updates to the NCCN Guidelines

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Abstract

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Prostate Cancer provide multidisciplinary recommendations for the clinical management of patients with prostate cancer. These NCCN Guidelines Insights highlight notable recent updates. Abiraterone acetate is a first-in-class hormonal agent that represents a new standard of care for patients with metastatic castration-recurrent prostate cancer who have previously received docetaxel (category 1 recommendation). Abiraterone acetate also received category 2B recommendations in the prechemotherapy setting for asymptomatic patients or symptomatic patients who are not candidates for docetaxel. The NCCN Prostate Cancer Panel also added new indications for existing agents, including the option of sipuleucel-T as second-line therapy. In addition, brachytherapy in combination with external beam radiation therapy with or without androgen deprivation therapy is now an alternative for patients with high-risk localized tumors or locally advanced disease. (*JNCCN* 2012;10:1081–1187)

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Disclosures for the NCCN Prostate Cancer Panel

Individual disclosures of potential conflicts of interest for the NCCN Prostate Cancer Panel can be found online at NCCN.org.

Please Note

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) are a statement of consensus of the authors regarding their views of currently accepted approaches to treatment. **The NCCN Guidelines® Insights highlight important changes in the NCCN Guidelines® recommendations from previous versions. Colored markings in the algorithm show changes and the discussion aims to further understanding of these changes by summarizing salient portions of the Panel's discussion, including the literature reviewed.**

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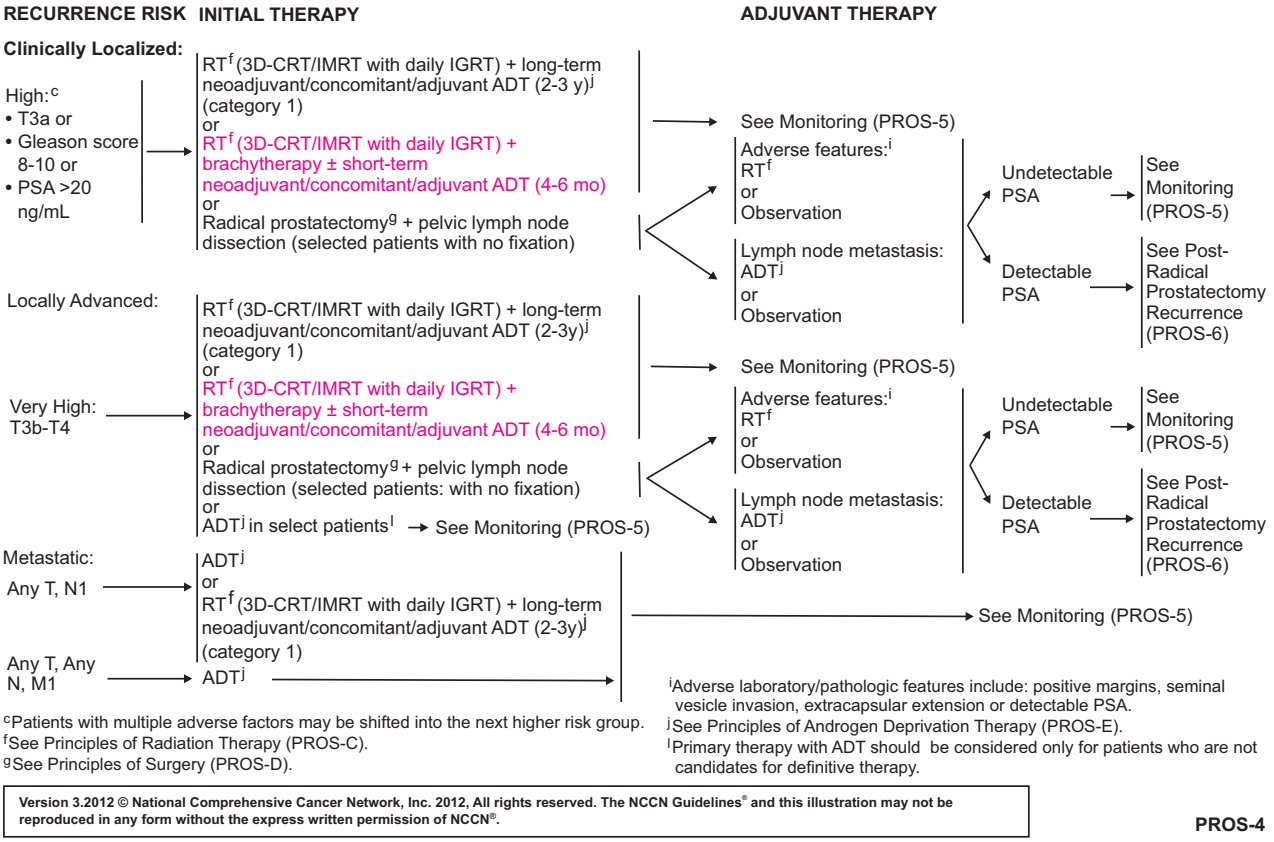
The full and most current version of these NCCN Guidelines is available at NCCN.org.



PROS-4

NCCN Categories of Evidence and Consensus

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.
Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.

Clinical trials: NCCN believes that the best management for any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

Overview

Prostate cancer has surpassed lung cancer as the most common cancer in men. These changes may result partly from the use of serum prostate-specific antigen (PSA) for early detection of prostate cancers that may include many very early tumors. An estimated 241,740 new cases will be diagnosed in 2012, accounting for 29% of new cancer cases in men in 2012.[1] Researchers estimate that prostate cancer will account for 28,170 deaths in 2012. The problem of overdiagnosis and overtreatment of early tumors is the subject of ongoing controversy fueled by large screening studies.[2–5] Depending on the disease characteristics and the patient's life expectancy and personal preference, active surveillance may be a viable alternative to immediate treatment with radical prostatectomy or radiation for slow-growing tumors. For patients with high-risk localized tumors or locally advanced disease, external beam radiation therapy (EBRT) with androgen deprivation therapy (ADT)

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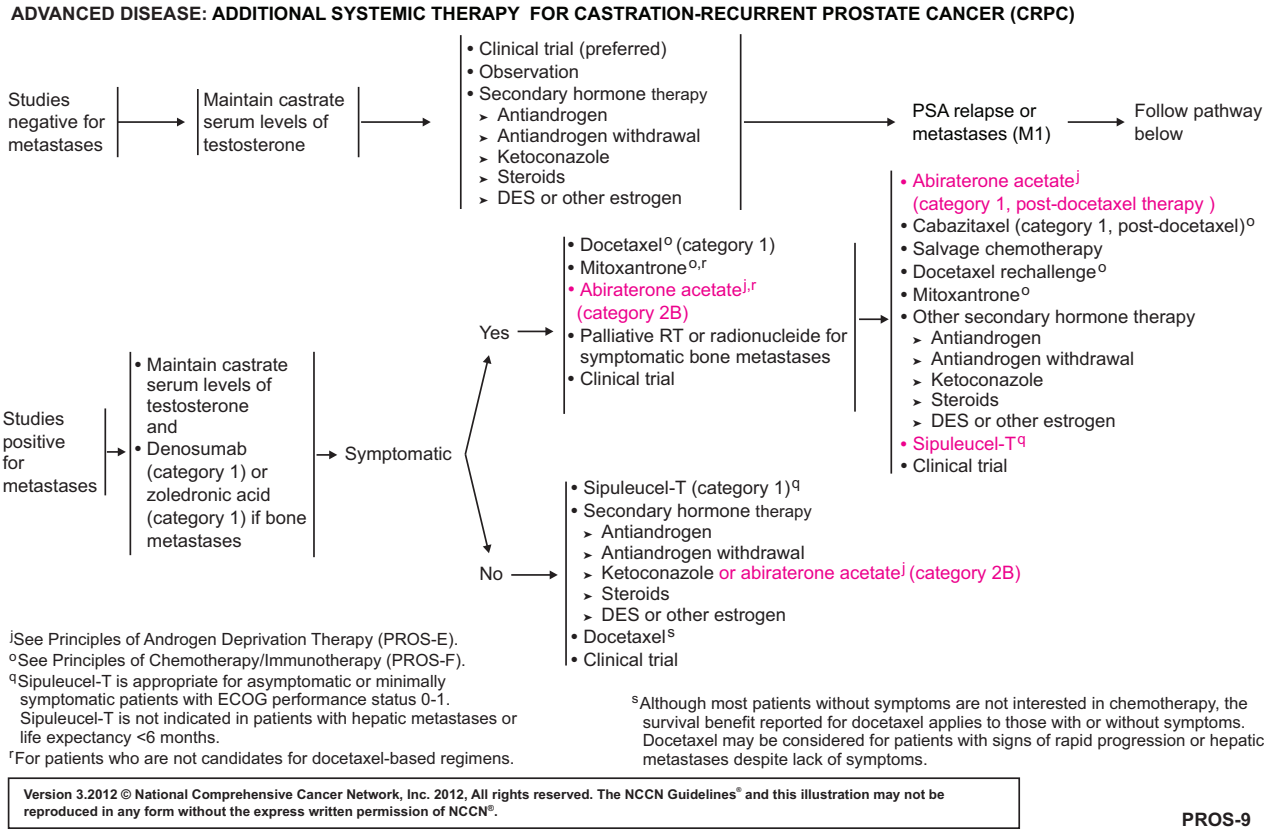

has traditionally been the main form of treatment. Increasing evidence supports the option of brachytherapy combined with EBRT with or without ADT for this group of patients. On the advanced-disease front, a recent surge in the development of novel agents has greatly expanded the armamentarium to treat and potentially prolong survival for patients with metastases after ADT has failed. These agents, including the hormonal therapy abiraterone acetate and immunotherapy sipuleucel-T, are welcome therapeutic additions for patients with late-stage disease who have a poor prognosis.

NCCN convened a multidisciplinary panel of leading experts at NCCN Member Institutions to develop and continually update guidelines for the treatment of prostate cancer. The latest full guideline, including a complete list of updates, is available on the NCCN Web site (NCCN.org). These NCCN Guidelines Insights highlight some of the major additions.

Brachytherapy for High-Risk Tumors and Locally Advanced Disease

Management of patients with high-risk or very-high-risk prostate cancer remains a challenge. Brachytherapy is not traditionally being used in these cases because earlier studies found it to be less effective than EBRT.[6,7] However, with technical advancements in recent years, the use of contemporary brachytherapy in high-risk localized and locally advanced prostate cancer is supported by increasing evidence.[8]

Brachytherapy involves placing radioactive sources into prostate tissue. There are 2 methods of prostate brachytherapy. Low-dose-rate (LDR) brachytherapy involves permanent seed implants widely used for low-risk cases. High-dose-rate (HDR) brachytherapy, which involves temporary insertion of the radiation source, is a newer approach that provides a "boost" dose in addition to EBRT for patients at high risk for recurrence. Through combining EBRT and HDR brachytherapy, one can es-

calate radiation doses while minimizing acute or late toxicity in patients with high-risk localized or locally advanced cancer.[9–12] Studies have shown a reduced risk of recurrence with the addition of brachytherapy to EBRT.[13–15] An analysis of a cohort of 12,745 high-risk patients found that treatment with brachytherapy (hazard ratio [HR], 0.66; 95% CI, 0.49–0.86) or brachytherapy plus EBRT (HR, 0.77; 95% CI, 0.66–0.90) lowered disease-specific mortality compared with EBRT alone.[16]

The addition of ADT to brachytherapy and EBRT is common for patients at high recurrence risk. The outcome of trimodality treatment is excellent, with 9-year progression-free survival and disease-specific survival rates reaching 87% and 91%, respectively.[17,18] However, whether the ADT component contributes to outcome improvement is unclear. D'Amico et al[19] studied a cohort of 1342 patients with a PSA greater than 20 ng/mL and clinical T3/T4 and/or Gleason score 8 to 10 disease. The addition of either EBRT or ADT to brachytherapy did not confer an advantage over brachytherapy alone. However, the use of all 3 modalities reduced prostate cancer-specific mortality compared with brachytherapy alone (adjusted HR, 0.32; 95% CI, 0.14–0.73). Other analyses did not find an improvement in failure rate when ADT was added to brachytherapy and EBRT.[20,21]

NCCN Recommendations

The combination of EBRT and brachytherapy, with or without ADT, is listed as a primary treatment option for patients with high-risk or very-high-risk prostate cancer (see PROS-4, on page 1082). The role of ADT in this setting remains unclear. A multicenter, phase III, randomized trial has been started to investigate the efficacy and safety of brachytherapy and EBRT with long- or short-term ADT for high-risk localized prostate cancer.[22]

Abiraterone Acetate for Metastatic Castration-Recurrent Prostate Cancer

It has long been known that prostate cancer is driven by androgens. ADT is the first line of systemic therapy for patients who present with advanced disease or who experience progression after localized treatment. Unfortunately, most patients eventually stop responding to ADT. The development and approval of abiraterone acetate, an oral androgen synthesis inhibitor, showed the importance of androgen signaling from nongonadal sources in castration-recurrent prostate cancer (CRPC). Research has shown enhancement of autocrine and/or paracrine androgen synthesis in the tumor microenvironment of men receiving ADT.[23,24] Abiraterone acetate inhibits a key enzyme, cytochrome P450 17A1 (CYP17A1), that metabolizes testosterone/dihydrotestosterone from weak adrenal androgens.[25] Clinical data showing the efficacy of abiraterone acetate in the metastatic CRPC setting redefined and expanded the role of hormone therapy in advanced prostate cancer. Similar anti-androgens in development, such as MDV3100, also reported encouraging results.[26]

Post-Docetaxel

The pivotal data for abiraterone acetate approval came from a phase III, randomized, placebo-controlled trial in men with metastatic CRPC previously treated with docetaxel-containing regimens.[27] Patients were randomized to receive either abiraterone acetate 1000 mg orally once daily (n = 797) or placebo once daily (n = 398), and both arms received daily prednisone. The study was unblinded after a prespecified interim analysis showed a statistically significant improvement in overall survival in patients receiving abiraterone acetate. The median survival was 14.8 versus 10.9 months in the abiraterone and placebo arms, respectively (HR, 0.65; 95% CI, 0.54–0.77; $P < .001$). Time to radiographic progression, PSA decline, and pain palliation also were improved by abiraterone acetate.

In general, abiraterone acetate is well tolerated. Common side effects (> 5%) were joint swelling or discomfort, hypokalemia, edema, muscle discomfort, hot flush, diarrhea, urinary tract infection, cough, hypertension, arrhythmia, urinary frequency, nocturia, dyspepsia, and upper respiratory tract infection. These were mostly grade 1 or 2 events. The most common adverse reactions resulting in drug discontinuation were increased aspartate aminotransferase and/or alanine aminotransferase, urosepsis, or cardiac failure (each in < 1% of patients taking abiraterone acetate). The most common electrolyte imbalances in patients receiving abiraterone acetate were hypokalemia (28%) and hypophosphatemia (24%).

Pre-Docetaxel

Phase I and II studies have shown activity in chemotherapy-naïve patients with CRPC.[28,29] Some panel-

ists find it reasonable to include abiraterone acetate as an option before docetaxel therapy. Others prefer to wait until data from an ongoing phase III trial are published.[30] This difference in opinion is reflected in the category 2B designation for the agent in the pre-chemotherapy setting for metastatic CRPC.

For patients showing no symptoms, secondary hormone therapy is an existing option. Given its favorable toxicity profile compared with ketoconazole, abiraterone acetate is added as an alternative (category 2B).

The panel acknowledges that some men with symptomatic metastatic CRPC are not candidates for docetaxel chemotherapy. In these men, abiraterone acetate with prednisone may be an appropriate therapy, given its survival and palliative benefit and reasonable toxicity (category 2B). However, the panel agreed that its routine use in the pre-docetaxel setting should be discouraged until high-level evidence from an ongoing randomized study of abiraterone acetate and prednisone versus placebo and prednisone in this setting has been published.[30] This trial has completed accrual, and initial results are expected soon.

NCCN Recommendations

The panel included recommendations for abiraterone acetate in the treatment of metastatic CRPC (see PROS-9, on page 1083). In the post-docetaxel setting, abiraterone acetate has shown clinical benefit in a phase III randomized trial and thus represents a new standard of care (category 1). Abiraterone acetate received category 2B recommendations for patients who are asymptomatic or are symptomatic but are not amenable to docetaxel therapy.

Abiraterone acetate should be given with a glucocorticoid (oral prednisone, 5 mg twice daily) to prevent side effects from increased levels of the adrenocorticotropic hormone (ACTH) that can result from the treatment. In addition, it should be taken in a fasting state because of higher levels of drug exposure when taken with food to abrogate signs of mineralocorticoid excess. These signs can include hypertension, hypokalemia, and peripheral edema. Serum electrolytes should be monitored closely during therapy. The panel recommends that patients be monitored closely with radiologic imaging (CT, bone scan), PSA tests, and clinical examinations for evidence of progression. In cases in which PSA or bone scan changes may indicate flare rather than true clinical progression, therapy should be continued until clinical progression or intolerability.[28] The sequential use of other agents, such as cabazitaxel,[31] is reasonable in patients who remain candidates for further systemic therapy.

Sipuleucel-T as Second-Line Therapy

The plethora of recently approved and upcoming novel agents for metastatic CRPC has presented new therapeutic possibilities. The optimal sequence and combination of ADT, immunotherapy, and chemotherapy has become a moving target in panel discussions.

Sipuleucel-T is a first-in-class autologous live cancer "vaccine" first approved in 2010 for asymptomatic or minimally symptomatic patients with metastatic CRPC. The pivotal study was a phase III, multicenter, randomized, double-blind trial in 512 patients.[32] Median survival in the vaccine arm was 25.8 months compared with 21.7 months in the placebo arm. Common complications, which include chills (54%), pyrexia (29%) and headache (16%), are typically mild and/or transient. Based on these data, sipuleucel-T has an existing category 1 recommendation in the pre-docetaxel setting. Notably, no effect on the time to disease progression was observed, and PSA responses were rare, which poses challenges in predicting and monitoring response.

The panel also discussed the role of this agent in patients exposed to chemotherapy. In the above trial, 18% of patients had received prior chemotherapy, which included docetaxel, because eligibility requirements included no chemotherapy for 3 months and no steroids for 1 month before enrollment.[32] These men were asymptomatic or minimally symptomatic. In a subset analysis, both those who did and did not receive prior chemotherapy (and otherwise met eligibility criteria) benefited from sipuleucel-T treatment. The combination and sequencing of sipuleucel-T in relation to other agents is being investigated in clinical trials.[33,34]

NCCN Recommendations

The panel added sipuleucel-T as a category 2A option after failure of, or treatment with, chemotherapy in asymptomatic or minimally symptomatic patients with good performance status (see PROS-9, on page 1083). Patients with rapidly progressing disease, liver metastasis, or life expectancy less than 6 months should not be considered for sipuleucel-T. Clinicians and patients should be aware that the common

markers of benefit, such as a decline in PSA or improvement in bone or CT scans, are not seen usually, and therefore benefit to an individual patient cannot be ascertained using currently available testing.

Conclusions

These NCCN Guidelines Insights highlight important updates to the management of prostate cancer in the NCCN Guidelines for Prostate Cancer. The NCCN Guidelines are updated at least annually, and more often when new high-quality clinical data become available in the interim. The most up-to-date version of these continuously evolving guidelines is available online at NCCN.org. The recommendations in the NCCN Guidelines are based on evidence from clinical trials when available, combined with expert consensus of the NCCN Guidelines Panel. Independent medical judgment is required to apply these guidelines individually to provide optimal care. The physician and the patient have the responsibility to jointly explore and select the most appropriate option from among the available alternatives. When possible, consistent with NCCN philosophy, the NCCN Guidelines Panel strongly encourages patient/physician participation in prospective clinical trials.

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