**PSA implications and medical management of prostate cancer for the primary care physician**

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Prostate cancer remains a common cancer diagnosis and cause of cancer-related death in men. Despite its high prevalence, screening for prostate cancer for early detection remains controversial. This article outlines evidence from contemporary prostate cancer screening clinical trials and presents an overview of therapeutic options across the spectrum of prostate-cancer states.

Key Words: prostate adenocarcinoma, prostate cancer, prostate cancer screening, prostate-specific antigen (PSA)

**Introduction**

Prostate cancer is the third leading cause of cancer-related mortality in Canada.\(^1\) Despite this high prevalence, screening for prostate cancer remains controversial due to conflicting clinical-trial evidence to support its widespread use. In Canada, primary care physicians remain at the forefront of discussing the potential benefits as well as the pitfalls of prostate cancer screening with men at risk. In this article, the term “prostate cancer screening” refers to an assessment of serum prostate-specific antigen (PSA) level along with a digital rectal examination (DRE).

**Epidemiology of prostate cancer**

While prostate cancer remains highly prevalent, the probability that a man with the disease will die from it is relatively low. In Canada, the lifetime probability of being diagnosed with prostate cancer is one in seven, while the associated risk of death is only one in 27.\(^1\) This discordance between prevalence of prostate cancer and risk of subsequent death is related to the relative indolence of many of the screening diagnosed cases. A study of incidental prostate cancer diagnosed in organ donors found prostate cancer in one in three men aged 60 to 69 years, but found prostate cancer in 46% of men over age 70.6 years.\(^2\)

**PSA**

Prostate-specific antigen (PSA) is a 33-kD glycoprotein that is secreted by prostate epithelial cells and functions to liquefy semen.\(^3\) Prostate cancer cells do not produce more PSA than normal prostate epithelial cells, but the disruption of epithelial cell architecture in prostate cancer results in an increased “leak” of PSA into the bloodstream.\(^3\) Other causes for elevated PSA include benign prostatic hyperplasia (BPH), prostatitis, urethral instrumentation, prostate biopsy, and ejaculation.\(^1\)
Controversies in prostate cancer screening
The widespread introduction of PSA testing has led to a significant migration in the prostate cancer stage at diagnosis—a higher proportion of men are being diagnosed at far earlier stages of the disease. Often cancers diagnosed from this type of screening carry little risk for mortality compared with other potential causes of death such as cardiovascular disease. The probability of “over-diagnosis” along with the possibility of unnecessary, aggressive “over-treatment” has resulted in the current prostate cancer screening controversy. Overtreatment of clinically and pathologically insignificant cancers has likely, to a large extent, also contributed to the conflicting data about survival benefits from screening.

The US Preventive Services Task Force (USPSTF) released a recommendation statement for screening for prostate cancer that was published in July 2012. Prostate cancer screening was given a grade D recommendation and the recommendation statement effectively discouraged its use. The main position of the USPSTF is that PSA screening results in overdiagnosis and that the potential harms related to prostate cancer screening outweigh the potential benefits.

This USPSTF recommendation statement, which updates a previous version issued in 2008, asserts that prostate cancer screening results in the detection of many cases of asymptomatic prostate cancer, and that a substantial percentage of men who have asymptomatic cancer detected by PSA screening have a tumor that either will not progress or will progress so slowly that it would have posed little threat as a competing risk for mortality. The potential benefit of PSA screening is the reduction in prostate cancer mortality 10 to 14 years later. On the other hand, the harms of screening include pain, fever, bleeding, infection, and transient urinary difficulties associated with prostate biopsy; the psychological harm of overdiagnosis of indolent disease; and the potential harms of treatment that include erectile dysfunction and urinary incontinence. Finally, USPSTF asserts that the inability to reliably distinguish tumors that will remain indolent from those destined to become lethal results in many men being subjected to the harms of treatment for indolent prostate cancer.

Evidence from screening trials
The results from two pivotal studies of prostate cancer screening were published in 2009. The European Randomized Study of Screening for Prostate Cancer (ERSPC) and the Prostate, Lung, Colon and Ovary (PLCO) trial of the National Cancer Institute were poised to elucidate the role of PSA screening. Unfortunately, their results have led to more confusion rather than clarity.

In the PLCO trial, 76,693 patients from 55 to 74 years of age were randomized to receive screening versus no screening. Randomization was performed in blocks, and men were stratified by age and center. Men in the investigation group received annual PSA screening tests, and those in the control group were not actively screened but some received screening outside the trial, which resulted in significant contamination. The primary study endpoint was cause-specific mortality for prostate cancer. Data on cancer incidence, cancer stage, and patient survival were collected for secondary study endpoints. At the 10 year follow up, there was no difference in mortality in the screened group versus the control group. However, there were a number of significant drawbacks and flaws in the study design that may explain this outcome. Contamination was a significant problem: 44% of the study subjects had PSA screening before the study (they were “pre-screened”), and 52% of the men in the control group had PSA testing performed outside of the study, at the discretion of their treating physicians.

The ERSPC study was a randomized, multicenter, multinational study of 182,160 men aged 50 to 74 years. The men were screened at 4 year intervals, except in Sweden where they were screened at 2 year intervals. A PSA level ≥ 4.0 ng/mL and an abnormal DRE were initially considered as indications for prostate biopsy in some centers; from 1997 on, all centers recommended a biopsy to men presenting with a PSA value ≥ 3.0 ng/mL. Biopsies were carried out within the ERSPC screening centers. The trial reported a 20% reduction in prostate cancer deaths. It was estimated that at 9 years of follow up, to prevent one death from cancer, 1,410 men would need to be screened (number needed to screen, NNS) and a further 48 would need to be treated (number needed to treat, NNT). A 2 year follow up study reported that to prevent one death from prostate cancer, the NNS was 936 and the NNT was 33. Like the PLCO trial, the ERSPC trial had a number of flaws. Screening practices varied across different study locations. The centers used different PSA thresholds for sending men for biopsies, and different PSA screening intervals. Many men were screened with intervals as long as every 4 years, which is significantly different from current practice. In addition, an estimated 20% of the control group was contaminated by off-protocol screening.

A third study from Goteborg, Sweden was reported in the Lancet in 2010. In that study, 20,000 patients were randomized to an intervention (screening) group...
or a control group. Men in the screening group were invited for screening every 2 years until they reached the study’s upper age limit (median 69 years, range 67-71 years), and only men with elevated PSA levels were offered additional tests such as DRE and prostate biopsies. The primary study endpoint was prostate-cancer-specific mortality, analyzed according to the intention-to-screen principle. Men with a PSA at or above a certain threshold were invited for further urologic work up; the threshold was 3.4 ng/mL from 1995-1998, 2.9 ng/mL from 1999-2004, and 2.5 ng/mL from 2005 onward. At 14 years of follow up, to prevent one death from prostate cancer, the NNT was 293 and the NNS was 12. There are several reasons why results from this study differed from those in the ERSPC and PLCO studies. Patients were generally younger (average age 54 years) with a lower PSA threshold for biopsy (originally 3.4 ng/mL, which was later lowered to 2.5 ng/mL) and with less PSA pre-screening (3%).

In addition, this trial included 14 years of follow up data, which provides mature, long term results. The current Canadian Urological Association guidelines recommend that the risks and benefits of prostate cancer screening must be discussed with the patient, so that a shared decision can be made about screening. Screening should be offered to all men 50 years old with at least a 10 year life expectancy. In addition, men at higher risk of prostate cancer (such as those of African descent or with a family history of prostate cancer) should be offered earlier screening at age 40.

**PSA measurement**

The usefulness of PSA as a screening tool to detect and diagnose prostate cancer is subject to a number of challenges. As previously mentioned, a number of physiologic states besides prostate cancer may affect the absolute level of serum PSA, and it is difficult to determine a specific cutoff level above which a prostate biopsy is necessary. The usefulness of PSA as a diagnostic tool may be improved by using adjunctive approaches, such as also measuring free PSA, PSA density, PSA velocity, and age-adjusted PSA, or by using 5-alpha reductase inhibitors (5-ARIs).

Adjusting PSA cutoffs according to age helps to detect more cancers in younger patients and fewer cancers in older men. Using a cutoff PSA velocity of greater than 0.75 ng/mL/year when a patient’s PSA is above 4 ng/mL may improve the sensitivity of cancer detection. PSA density allows for adjustment of PSA level according to prostate volume. A PSA density greater than 0.15 ng/mL may be associated with an increased risk of prostate cancer. However, a PSA density assessment is not as convenient as a simple PSA test, since it requires transrectal ultrasonography to accurately measure the prostate volume. The use of a ratio of free PSA to total PSA improves PSA specificity. Men with higher ratios are more likely to have benign disease.

5-ARIs are known to decrease serum PSA levels and improve PSA kinetics. The decrease in PSA levels by 5-ARIs must be taken into account when judging the significance of a PSA measurement. In the Prostate Cancer Prevention Trial (PCPT), finasteride lowered the PSA by 50% after 12 months of therapy, and therefore, a multiplier of 2 was used as a criterion for biopsy. Preliminary analyses of the Reduction by Dutasteride of Prostate Cancer Events (REDUCE) trial also suggest that dutasteride enhances the performance of PSA as a diagnostic test for prostate cancer.

A number of nomograms can be used to help assess the risk of prostate cancer. These risk assessment tools take into account variables such as DRE, PSA, PSA velocity, PSA isoforms, age, race, family history of prostate cancer, and genetic data to determine a man’s risk of prostate cancer and the risk of biologically significant disease. Using such a multivariate model better predicts the risk of prostate cancer when compared to PSA alone.

**Prostate cancer chemoprevention trials**

The PCPT and REDUCE trials are two key, contemporary chemoprevention studies. The PCPT trial randomized 18,882 men aged 55 years or older to finasteride 5 mg po daily versus placebo, and the primary study endpoint was the incidence of prostate cancer over the study period. The study reported a 24.8% reduction in diagnosed prostate cancer in the treated cohort. However, while most of this was due to a decrease in low grade tumors, the prevalence of high grade tumors (Gleason grade 7 to 10) was slightly higher in the finasteride group than in the placebo group (6.4% versus 5.1%). The potential induction of high grade disease by finasteride has been the subject of much controversy. In general, it is felt that the drug does not cause the high grade cancer, but rather, a reduction in the volume of the prostate gland caused by finasteride may render random biopsies more effective in detecting foci of high grade disease. Nonetheless, this finding has resulted in a general tendency to avoid the use of finasteride for chemoprevention of prostate cancer.

The REDUCE trial randomized 8,231 patients to either treatment with dutasteride 0.5 mg po daily or a placebo. The study participants were men aged 50 to 75 years old, with PSA scores from 2.5 ng/mL to 10 ng/mL.
prostate volumes less than or equal to 80 cc, and one prior negative prostate biopsy within 6 months of enrollment (thus representing a group at high risk for cancer on subsequent biopsy). The primary endpoint of REDUCE was the prevalence of cancer on study-mandated prostate biopsies performed at 2 and 4 years after study entry. Important differences between the PCPT and REDUCE trials were principally, that patients in REDUCE were mandated to have a negative biopsy at enrollment. In addition, the REDUCE trial included patients with a higher PSA range at study entry (2.5 ng/mL-10 ng/mL). The PCPT trial, on the other hand, included patients at lower risk (PSA less than 3 ng/mL). The REDUCE study demonstrated a relative risk reduction of prostate cancer of 22.8% over 4 years. The largest reduction in cancers was again noted in the low grade tumors. An increase in high grade cancers was also noted, but this did not reach statistical significance (19 in the placebo arm versus 29 in the dutasteride arm, p = 0.15).

Treatment of localized prostate cancer

There are a multitude of therapeutic clinical options currently available for patients who have early, organ-confined prostate cancer. These include three gold standard therapies—active surveillance (with selective, delayed intervention, if necessary); radical prostatectomy (retropubic, laparoscopic, or robotic); and radiation therapy (e.g., external beam radiotherapy, brachytherapy)—as well as other options such as cryotherapy and high intensity focused ultrasound (HIFU).

**Active surveillance**

Active surveillance was conceived with the aim of reducing overtreatment in patients with organ-confined, low risk prostate cancer. This is based on early clinical trials demonstrating that men with well-differentiated tumors have a 20 year prostate-cancer-specific survival rate of 80% to 90%. If the detected prostate cancer is not expected to affect overall survival, active surveillance is a viable management option. This implies close follow up with the option for curative therapy upon evidence of disease progression. It is important to differentiate active surveillance from “watchful waiting.” The latter is essentially deferred treatment until the development of local or systemic symptoms. At that point, the patient would be treated palliatively, with local or systemic management.

**Surgical management**

Radical prostatectomy can be performed with open retropubic; laparoscopic; or robotically-assisted approaches. The main advantages of radical prostatectomy are the possibility for a cure, the ability for accurate pathological staging, and the possibility of offering the patient potential salvage therapy with radiation, if necessary. An ideal candidate for radical prostatectomy is a healthy man with a life expectancy of at least 10 years. Preoperative clinical and pathologic parameters are often used to attempt to identify patients most likely to benefit from surgery. The principal disadvantages of surgery include possible urinary incontinence and/or erectile dysfunction. However, with improved understanding of the male pelvic floor anatomy and improved surgical approaches, great strides have been made in reducing adverse outcomes.

**Radiation therapy**

Radiotherapy is offered as either brachytherapy, external beam radiotherapy (EBRT), or a combined approach. Brachytherapy involves radioactive seeds that are implanted directly into the prostate gland to deliver high doses of radiation to the prostate while sparing adjacent structures. EBRT uses gamma radiation beams directed at the prostate and surrounding tissues through multiple fields. High risk patients are typically administered a limited course of androgen deprivation therapy prior to, during, and after EBRT.

**Cryoablation and HIFU**

Newer treatment options other than the above-mentioned, gold standard treatments for localized prostate cancer include cryoablation, and high intensity focused ultrasound (HIFU). Cryotherapy, which involves freezing the prostate under direct vision, has also been studied as a salvage option in cases of radiation failure. HIFU consists of focused ultrasound waves, which cause tissue damage by mechanical and thermal effects. HIFU is an experimental procedure that can be used as primary therapy or as a salvage option. The US Food and Drug Association has an ongoing trial to determine if HIFU can be used as a salvage option in patients who have failed primary external beam radiation treatment for prostate cancer.

**Treatment for metastatic prostate cancer**

**Hormone manipulation**

Prostate cancer cellular growth is mediated by testosterone and dihydrotestosterone, under the control of the hypothalamic-pituitary axis. Release of gonadotropin-releasing hormone by the hypothalamus to the anterior pituitary promotes luteinizing hormone secretion and subsequent testosterone production in
Androgen deprivation can be achieved either by suppressing the secretion of testicular androgens by surgical or medical castration, or by inhibiting the action of circulating androgens on receptors in prostate cells by using antiandrogens. The most common method of hormone manipulation is medical castration by administering luteinizing hormone-releasing hormone (LHRH) agonists, LHRH antagonists, or antiandrogens. See Table 1 for a list of LHRH agonists and LHRH antagonists. See Table 2 for a list of antiandrogen hormonal therapies for prostate cancer. In recent years, there has been concern about side effects from androgen deprivation therapy. Common side effects include loss of lean muscle mass, hot flashes, loss of bone mineral density, decreased libido (and erectile dysfunction), cognitive

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<tr>
<th>Name (Brand name)</th>
<th>Class</th>
<th>Administration</th>
<th>Notes</th>
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<tbody>
<tr>
<td>Buserelin (Suprefact [Canada only])</td>
<td>LHRH agonist</td>
<td>SC: 500 mcg q8h X 7 days then 200 mcg daily; Depot 2-month: 6.3 mg implant every 8 weeks Depot 3-month: 9.45 mg implant every 12 weeks Intranasal: 400 mcg (200 mcg into each nostril) 3 times/day</td>
<td>Can cause initial hormonal surge</td>
</tr>
<tr>
<td>Degarelix (Firmagon)</td>
<td>LHRH antagonist</td>
<td>Starting dose: 240 mg SC in 2 divided doses. Maintenance dose: 80 mg SC every month, first dose given one month after starting dose</td>
<td>No hormonal surge; administer in abdominal wall</td>
</tr>
<tr>
<td>Goserelin acetate (Zoladex, Zoladex LA)</td>
<td>LHRH agonist</td>
<td>3.6 mg SC monthly (28 days); 10.8 mg SC every 3 months (13 weeks)</td>
<td>Can cause initial hormonal surge; SC resorbable implant</td>
</tr>
<tr>
<td>Histrelin (Vantas [US only])</td>
<td>LHRH agonist</td>
<td>SC implant 50 mg every 12 months</td>
<td>Remove implant at reinserion; local anesthesia, place in upper inner arm</td>
</tr>
<tr>
<td>Leuprolide (Lupron Depot)</td>
<td>LHRH agonist</td>
<td>7.5 mg IM monthly; 22.5 mg IM every 3 months; 30 mg IM every (16 weeks)</td>
<td>Can cause initial hormonal surge</td>
</tr>
<tr>
<td>Leuprolide gel (Eligard)</td>
<td>LHRH agonist</td>
<td>7.5 mg SC monthly; 22.5 mg SC every 3 months; 30 mg SC every 4 months; 45 mg SC every 6 months</td>
<td>Can cause initial hormonal surge; requires refrigerated storage</td>
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<tr>
<td>Leuprolide implant (Viadur [US, not Canada])</td>
<td>LHRH agonist</td>
<td>SC implant every 12 months (contains 65 mg leuprolide)</td>
<td>Off US market for new patients since 2008</td>
</tr>
<tr>
<td>Triptorelin (Trelstar, Trelstar LA)</td>
<td>LHRH agonist</td>
<td>3.75 mg IM monthly; 11.25 mg IM every 3 months; 22.5 mg IM every 6 months (US only)</td>
<td>Can cause initial hormonal surge</td>
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TABLE 2. Antiandrogen hormonal therapy for prostate cancer

<table>
<thead>
<tr>
<th>Name (Brand name)</th>
<th>Class</th>
<th>Administration</th>
<th>Notes</th>
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<tbody>
<tr>
<td>Flutamide (Euflex [Canada], Eulexin [US])</td>
<td>Nonsteroidal antiandrogen</td>
<td>250 mg po every 8 hours w/ LHRH analog</td>
<td>Follow LFTs</td>
</tr>
<tr>
<td>Nilutamide (Anadron [Canada]) (Nilandron [US])</td>
<td>Nonsteroidal antiandrogen</td>
<td>Start at 300 mg po daily x 30 days then 150 mg po daily w/ LHRH analog or orchiectomy</td>
<td>Follow LFTs Baseline PFTs</td>
</tr>
<tr>
<td>Bicalutamide (Casodex)</td>
<td>Nonsteroidal antiandrogen</td>
<td>50 mg po daily w/ LHRH analog</td>
<td>Follow LFTs</td>
</tr>
<tr>
<td>Cyproterone acetate (Androcur, Androcut Depot [Canada only])</td>
<td>Steroidal antiandrogen</td>
<td>100 mg-300 mg po daily, divided into 2-3 doses (after meals) 300 mg IM weekly or 300 mg IM q2weeks (if orchiectomized)</td>
<td>Follow LFTs</td>
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LFTs = liver function tests

impairment, and cardiovascular compromise. Some adverse effects of hormonal therapies may be mitigated by intermittent and judicious use of these agents and by careful patient monitoring.

Chemotherapy

Castrate resistant prostate cancer (CRPC) is defined as disease progression despite having achieved an acceptable castrate testosterone level, and it may present as either a continuous rise in serum PSA levels, progression of pre-existing disease, and/or the appearance of new metastases. Patients with CRPC and macroscopic metastatic disease are considered to be candidates for systemic chemotherapy. Current chemotherapeutic options are rapidly expanding beyond docetaxel (Taxotere).

Cabazitaxel (Jevtana), a novel taxane, in combination with prednisone, is approved for the treatment of patients with metastatic CRPC who failed docetaxel-based chemotherapy. Abiraterone (Zytiga) is a new oral androgen biosynthesis inhibitor indicated for use in combination with prednisone for the treatment of metastatic prostate cancer (CRPC) in patients who have received prior chemotherapy containing docetaxel. Abiraterone inhibits the CYP17 enzyme which is required for androgen biosynthesis in testicular, adrenal and prostatic tumor tissues, reducing serum testosterone and other androgens to levels lower than that achieved with LHRH agonists alone or orchiectomy. A recent clinical trial concluded that abiraterone prolongs overall survival among patients with metastatic prostate cancer who previously received chemotherapy with docetaxel. Enzalutamide (Xtandi) is an oral androgen receptor inhibitor recently approved in the United States for the treatment of patients with metastatic CRPC who have previously received docetaxel, and may be given with or without prednisone. See Table 3 for a list of chemotherapies for CRPC and other agents for treating skeletal-related events secondary to advanced prostate cancer or CRPC.

A host of other highly promising agents are under intense investigation and are poised to improve the prognosis of patients with advanced disease. The introduction of new therapeutic options also promises to create a paradigm shift in the timing of chemotherapy as well as the combination and sequencing of agents to extend survival.

Conclusion

Prostate cancer screening remains controversial. Primary care physicians should discuss the potential benefits and pitfalls of early diagnosis of prostate cancer with patients who have at least a 10 year life expectancy. The choice to pursue prostate cancer screening must be made after careful consideration of the implications of a positive diagnosis.

Disclosure

The authors have no potential conflict of interest.
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<thead>
<tr>
<th>Name (Brand name)</th>
<th>Dose</th>
<th>Mechanism</th>
<th>Side effects/Notes</th>
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<tr>
<td><strong>Prevention of skeletal related events in patients with bone metastases</strong></td>
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<tr>
<td>Zoledronic acid (Zometa)</td>
<td>4 mg IV infusion over 15 min every 3-4 weeks</td>
<td>Bisphosphonate</td>
<td>Reduce dose in patients with renal insufficiency; rare reports of osteonecrosis of the jaw; given with Vitamin D and calcium supplementation (indicated for treatment of bone metastases only in Canada)</td>
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<tr>
<td>Denosumab (Xgeva)</td>
<td>120 mg every 4 weeks SC</td>
<td>Monoclonal antibody targeting RANKL</td>
<td>Severe hypocalcemia can be seen; reports of osteonecrosis of the jaw; given with Vitamin D and calcium supplementation (Note there is different formulation/ dosing than denosumab [Prolia] used in female osteoporosis)</td>
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<tr>
<td><strong>Treatment of CRPC</strong></td>
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<td>Docetaxel (Taxotere)</td>
<td>75 mg/m² IV infusion over 1 hour every 3 weeks Given in combination with 5 mg prednisone po twice daily</td>
<td>Suppresses microtubule assembly dynamics</td>
<td>Should not be given in patients with elevated LFTs or who are neutropenic; severe fluid retention can also result</td>
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<tr>
<td>Cabazitaxel (Jevtana)</td>
<td>25 mg/m² IV infusion over 1 hour every 3 weeks Given in combination with 10 mg prednisone po once daily</td>
<td>Same as for docetaxel</td>
<td>Contraindicated in neutropenic patients or those with previous hypersensitivity; renal and GI toxicity reported</td>
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<td>Sipuleucel-T (US only)</td>
<td>Leukapheresis process 2-3 days prior to each dose to collect patient’s own immune cells; IV infusion in 3 doses given 2 weeks apart</td>
<td>Utilizes patients own immune cells to target cancer cells</td>
<td>Fevers; chills; fatigue; weakness; respiratory issues; dizziness; headache; GI upset all reported</td>
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<td>Abiraterone (Zytiga)</td>
<td>1 g (4 x 250 mg tabs) po once daily, taken on an empty stomach. Given in combination with low dose prednisone (10 mg po daily)</td>
<td>Androgen biosynthesis inhibitor</td>
<td>Myopathy, joint pain, hot flushes, diarrhea, urinary tract infection, cough. Increases mineralocorticoid production by adrenals and may cause hypertension, hypokalemia, fluid retention. Use with caution in patients with CV disease</td>
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<tr>
<td>Enzalutamide (Xtandi, [US only])</td>
<td>160 mg (4 x 40 mg caps) po once daily, taken during or before meals. Given with or without prednisone</td>
<td>Androgen receptor inhibitor</td>
<td>Weakness, fatigue, back pain, diarrhea, musculoskeletal and joint pain, hot flushes, headache, respiratory infections, dizziness, anxiety, hypertension. 1% of patients in clinical trial experienced seizure</td>
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References


