METASTATIC PROSTATE CANCER

Executive Summary
Prostate cancer, with an estimated 1.1 million new cases and over 300,000 deaths annually, is the second most common cancer among men globally. Although the majority of patients in resource-abundant regions are diagnosed with localized (and potentially curable) disease, patients in resource-limited regions typically present with advanced disease.

Androgen deprivation, via either surgical or medical castration, is the mainstay for advanced disease. Both options are equally efficacious and multiple randomized trials have documented improvements in disease progression with the use of androgen deprivation (32% progression in 10 years versus 62% on the placebo group). Surgical castration, via bilateral orchiectomy, is a more cost effective option and overcomes the barriers of medication non-compliance and access to healthcare. The primary forms of medical castration are gonadotropin releasing hormone (GNRH) agonists, available in depot formulations with a treatment effect lasting 1-6 months. Either surgical or medical options are recommended as the primary treatment for metastatic prostate cancer.

The effect of androgen suppression on prostate cancer progression is finite and the disease will eventually progress from “castrate sensitive” to “castrate resistant”. Castrate resistant prostate cancer, potentially treated with the addition of chemotherapy, is characterized by a median overall survival of between 1 and 2 years.

Public Health Relevance
Prostate cancer is known to be the sixth most common cancer in the world and the third most common cancer among men. GLOBOCAN estimates worldwide incidence of prostate cancer in 2012 to be 1,111,689 (ASR of 31.1 per 100,000). Incidence in more developed regions is 758,739 (ASR of 125.2 per 100,000) compared with an incidence of 352,950 (ASR of 12.0 per 100,000) in less developed regions. According to GLOBOCAN, the Eastern European region has the greatest incidence of prostate cancer (ASR of 99.9 per 100,000) followed by the Americas (ASR of 87.6 per 100,000).

GLOBOCAN approximates worldwide mortality rate of prostate cancer in 2012 to be 30,7471 (ASR of 7.8 per 100,000). Mortality rate in more developed regions in 2012 is 142,004 (ASR of 10.0 per 100,000) compared with a mortality rate of 165,467 (ASR of 6.6 per 100,000) in less developed regions. Like incidence, mortality rate is highest in the Eastern European region (ASR of 23.2 per 100,000) followed by the Americas (ASR of 18.1 per 100,000).

According to a study published in 2003, the mean age of men with prostate cancer is 72 to 74 years. There are great variations in the prevalence of this disease across geography and ethnicity, which may be attributed to differences in genetic susceptibility or external factors,
such as environment and differences in health care. Unfortunately, there is limited information available on the specific epidemiology of metastatic prostate cancer.

**Requirements for diagnosis, treatment, and monitoring**

**Diagnostics:**
The diagnosis of prostate cancer is most often made by histologic examination of a biopsy of the primary tumor/prostate gland (common) or metastasis (less common) using hematoxylin-eosin (H&E) staining. Needle core biopsy of the prostate is often performed with imaging assistance (e.g. transrectal ultrasound); a minimum of 12 cores are typically obtained to reduce sampling error. However, in the setting of advanced disease a biopsy of a distant metastatic site can confirm extra-prostatic disease.

A surgeon usually performs the prostate biopsy under local anesthesia. In addition to a morphologic description, the pathologist should grade the cancer using the Gleason grading system which not only characterizes the architecture of the prostate cancer but also provides prognostic information.

Serum prostate specific antigen (PSA) serves as a sensitive but not specific tumor marker, carrying both diagnostic and prognostic information. If the PSA is elevated, imaging studies (plain radiographs, ultrasound, radionuclide bone scan and/or CT scan or MRI) can clarify potential sites of distant disease. A rise in PSA during treatment indicates the need for further testing and/or treatment. Imaging studies should also be directed toward symptomatic areas (e.g. back pain, bone pain) and again can confirm the presence of metastatic disease.

Metastatic disease is further classified depending on the site of disease (e.g. regional lymph node involvement, non-regional lymph node involvement, involvement of the bone, or involvement of another site).

On occasion, a presumptive diagnosis of metastatic prostate cancer can be reasonably made based on concurrent findings of widespread metastatic disease in an expected distribution (e.g. bones, lymph nodes) along with a markedly elevated PSA (hundreds-thousands range), particularly if a biopsy is not able to be performed or reasonably evaluated by an experienced individual.

**Testing**
Once the diagnosis of metastatic prostate cancer has been established the following labs should be obtained: PSA, comprehensive metabolic panel to assess renal and hepatic function, and complete blood count. For patients actively undergoing therapy with androgen deprivation, PSA is monitored every 3 to 6 months. If PSA is rising, a serum testosterone should be obtained to determine if therapy is suppressing testosterone into the castrate range. Rising PSA despite castrated levels of testosterone reflects the development of “castration resistant” prostate cancer, the lethal form of advanced prostate cancer.
Administration and Care of Patients:
The initial treatment for patients with castration sensitive metastatic prostate cancer is androgen deprivation therapy (ADT) given the role of testosterone in the pathogenesis of prostate cancer. Androgen deprivation can be induced either medically or surgically (i.e. orchiectomy) with equivalent efficacy, however bilateral orchiectomy is a more cost effective option.\textsuperscript{5,6}

Bilateral surgical orchiectomy, the removal of both testicles via a scrotal incision, should be performed by a trained surgeon under sterile operating procedures. This procedure, performed as an outpatient, immediately reduces testosterone level and may be particularly useful when testosterone reduction is needed urgently.

Gonadotropin releasing hormone (GnRH) agonists are the mainstay of medical castration and achieve a similar reduction in serum testosterone as surgical orchiectomy.\textsuperscript{7,8} GnRH agonists result in the down-regulation of luteinizing and follicular stimulating hormones, however, initiation of treatment with GnRH agonists may result in a surge of testosterone.\textsuperscript{7} Consequently, a short course of an oral anti-androgen, such as bicalutamide, is recommended at the initiation of therapy to prevent transient worsening of cancer related symptoms, such as urinary retention or pain, that are considered “flare” responses.\textsuperscript{6,9}

GnRH agonists are administered either intramuscularly or subcutaneously and the duration of effect varies by formulation (typically 1-6 months). Patients should be monitored for local reactions (including allergic skin reactions) as well as adverse effects secondary to androgen deprivation (discussed below). Importantly, patients should be monitored for the behavioral and neurologic effects of ADT including depression.

The PSA should be measured every 3-6 months. Although most patients will respond to ADT, the effect of ADT is finite, and the cancer will subsequently progress by PSA, imaging or worsening of cancer-related symptoms despite castrate levels of testosterone (castration resistant prostate cancer, CRPC).

Early use of docetaxel has been shown to add benefit when added to GnRH agonists and bicalutamide, though this has been presented in abstract form and a peer-reviewed publication is not yet available.

Additional treatment options for CRPC include therapies targeting the androgen pathway (abiraterone and enzalutamide), immunotherapy (sipuleucel-T), and radiopharmaceuticals (radium-223). However, these agents are still in development and currently have shown a relatively small magnitude of benefit and their current costs limit the use of these agents in resource-limited settings. Therefore they are not recommended to be added to the EML.

A phase II trial and other small series have shown a benefit of using low dose conjugated estrogens (DES or fosfestrol) along with warfarin therapy with PSA responses of up to 79%. This has been recommended as an alternative second line manipulation in resource deprived regions that do not have access to other standard medications.\textsuperscript{20-23}
Notably, a recent trial suggested a significant overall survival benefit of the early initiation of docetaxel chemotherapy, in addition to ADT, among patients with castrate sensitive disease compared to ADT alone.\textsuperscript{10} The overall survival benefit was particularly profound among patients with high-volume metastatic disease (49.2 months vs. 32.2 months), which may be more characteristics among patients in resource-limited regions.

**Overview of Regimens**

The following tables include basic information on administration and dosing for androgen deprivation therapy with surgical orchietomy and LHRH agonists.

**Surgical Option for Castrate Sensitive Metastatic Prostate Cancer when LHRH agonists are not available or affordable**

<table>
<thead>
<tr>
<th>ADT: Bilateral Orchietomy and supportive measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgical orchietomy</td>
</tr>
<tr>
<td>Calcium Oral</td>
</tr>
<tr>
<td>1000 mg daily</td>
</tr>
<tr>
<td>Vitamin D Oral</td>
</tr>
<tr>
<td>2000 IU daily</td>
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</tbody>
</table>

**Standard Regimens for Castrate Sensitive Metastatic Prostate Cancer**

<table>
<thead>
<tr>
<th>ADT: LHRH Agonist (when bicalutamide is not available)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leuprolide Intramuscular injection 7.5 - 22.5mg q 1-3 months</td>
</tr>
<tr>
<td>Calcium Oral 1000 mg daily</td>
</tr>
<tr>
<td>Vitamin D Oral 2000 IU daily</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>ADT: LHRH Agonist</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leuprolide Intramuscular injection 7.5 - 22.5mg q 1-3 months</td>
</tr>
<tr>
<td>Bicalutamide Oral 50 mg daily for first two weeks</td>
</tr>
<tr>
<td>Calcium Oral 1000 mg daily</td>
</tr>
<tr>
<td>Vitamin D Oral 2000 IU daily</td>
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</tbody>
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*Note: Leuprolide is recommended to be added to the EML as a class agent, to include similar LHRH agonists*
Regimen for Castrate Sensitive Metastatic Prostate Cancer with high-volume of disease (i.e. visceral metastases and/or four or more bone metastases)\textsuperscript{10}

| Regimen for Castrate Sensitive Metastatic Prostate Cancer with high-volume of disease (i.e. visceral metastases and/or four or more bone metastases)\textsuperscript{10} |
|------------------|------------------|------------------|
| **ADT plus Docetaxel** | **Leuprolide** | **Intramuscular injection** | **22.5 mg q3 months** |
| **Bicalutamide** | **Oral** | **50 mg daily for first two weeks** |
| **Docetaxel** | **IV** | **75 mg/m2 q 3 weeks x 6-9 cycles** |
| **Dexamethasone** | **Oral** | **8 mg orally twice daily for 3 days beginning the day prior to docetaxel for patients not receiving prednisone** |
| **Calcium** | **Oral** | **1000 mg daily** |
| **Vitamin D** | **Oral** | **2000 IU daily** |

Alternative Regimen (for use when LHRH agonists not available or affordable)

- **Diethylstilbesterol (DES) Oral** 1-3 mg daily (in conjunction with warfarin therapy)

Review of Benefits and Harms

Benefits
Androgen deprivation, initially performed via orchiectomy, has been a recognized treatment for prostate cancer for approximately 75 years once the role of testosterone in the pathogenesis of prostate cancer was elucidated.

Orchiectomy: Data from the Veterans Affairs Research Service Cooperative Urological Research Group revealed that progression from extra-prostatic extension to distant metastases within 10 years was significantly improved in men receiving orchiectomy (32%) versus placebo (62%\{11}). This cooperative group also found an increased 5 year overall survival among the treatment arm (32%) versus placebo (20%).\textsuperscript{12} The benefits of surgical treatment over medical androgen deprivation include cost and patient adherence.

LHRH agonists: Multiple studies have compared LHRH agonists with surgical orchiectomy. A systematic review covering 10 randomized trials and nearly 2000 men found no difference among LHRH agonists versus surgical orchiectomy (hazard ratio, 1.1262 [corrected] [95% CI, 0.915 to 1.386]).\textsuperscript{5} In part due to patient preference, LHRH agonists are often the first line of therapy. Indeed in a multi-institutional study, nearly 80% of patients preferred treatment with a LHRH agonist over surgical castration.\textsuperscript{13}

In addition to yielding a survival benefit, the use of immediate treatment via either surgical orchiectomy or LHRH agonists was associated with decreased risk of pathologic fracture, spinal cord compression, and ureteric obstruction.\textsuperscript{14}
Harms and Toxicity Considerations
Adverse effects of ADT include sexual dysfunction, vasomotor symptoms (e.g. hot flashes), anemia, behavioral and neurologic effects, diabetes, cardiovascular disease, and decreased bone density. Given the risk of osteoporosis and pathologic fracture, a baseline measurement of bone density is recommended, as is calcium and vitamin D supplementation and exercise.\(^{15}\) The anemia is typically mild and usually does not necessitate specific therapy. Vasomotor symptoms can be treated supportively.

In order to minimize the side effects of ADT, researchers attempted to compare intermittent with continuous androgen deprivation. The results were inconclusive and continuous therapy remains the standard of care.\(^{16}\) A meta-analysis also revealed that the early initiation of ADT decreased prostate cancer related mortality (but not overall survival) and is also commonly practiced.\(^{17}\)

Other than the adverse effects of ADT described above, risks of surgical orchiectomy include blood loss, hematoma, and infection. Patients typically fully recover from surgery in 2-4 weeks.

Patients receiving docetaxel frequently experience dose-limiting neutropenia. Docetaxel is also associated with fluid retention ranging from mild peripheral edema to severe fluid retention and pleural effusion. Patients should be medicated with a corticosteroid before and after docetaxel doses to reduce this risk.\(^{18}\) Hypersensitivity reactions to docetaxel occur frequently but incidence is reduced to <5% with corticosteroid premedication.\(^{19}\) Patients may also experience sensory neuropathy, although this is generally mild and reversible.

Systematic Reviews


Aims: Since 2004, docetaxel-based chemotherapy has been the standard of care for men with metastatic castration-resistant prostate cancer(mCRPC), but recently randomised controlled trials (RCTs) of novel agents have shown promise in extending overall survival. These trials have evaluated agents delivered before chemotherapy, to replace or supplement docetaxel, or addressed treatment options for men who have progressed on docetaxel therapy. This review was undertaken to determine which systemic therapies improve cancer- or patient-related outcomes in men with mCRPC. Materials and Methods: Searches were carried out in MEDLINE, EMBASE, the Cochrane Library and relevant conference proceedings. Eligible articles included RCTs comparing systemic therapy or combination (excluding primary or secondary androgen deprivation therapy, bone protective agents or radionuclides) with placebo or other agents in men with mCRPC. Results: Twenty-five RCTs met the selection criteria. In chemotherapy-naive patients, targeted therapy with tasquinimod conferred a benefit in progression-free survival. Immunotherapy with sipuleucel-T extended overall survival and was well tolerated, but had no effect on the time to disease progression. Hypercastration with abiraterone extended progression-free survival, whereas overall survival was improved but not statistically proven. In the chemotherapy setting, updated and new trials of docetaxel alone confirmed the survival benefit seen in previous studies. A survival benefit with the addition of
estramustine to docetaxel shown in a previous study did not lead to an improvement in pain palliation or quality of life. Trials of combining targeted therapies with docetaxel generally did not extend survival. The addition of bevacizumab improved progression-free survival, but not overall survival. The addition of GVAX immunotherapy or calcitriol was harmful. In the post-chemotherapy setting, progression-free and overall survival benefits were detected with cabazitaxel, abiraterone and enzalutamide. Cabazitaxel was associated with greater toxicity, whereas abiraterone and enzalutamide had less severe adverse effects. Satraplatin and sunitinib both extended progression-free survival, but did not improve overall survival. Conclusion: Docetaxel-based chemotherapy remains the standard of care in men with mCRPC who are candidates for palliative systemic therapy. Promising results are emerging with sipuleucel-T and abiraterone in the pre-docetaxel setting and cabazitaxel, abiraterone and enzalutamide in patients who progress on or after docetaxel. Further research to determine the optimal choice, sequence or even the combination of these agents is necessary.


**Purpose:** To compare luteinizing hormone-releasing hormone (LHRH) agonists with orchiectomy or diethylstilbestrol, and to compare antiandrogens with any of these three alternatives. **Data Sources:** A search of the MEDLINE, Cancerlit, EMBASE, and Cochrane Library databases from 1966 to March 1998 and Current Contents to 24 August 1998 for articles comparing the outcomes of the specified treatments. The search was limited to studies on prostatic neoplasms in humans. Total yield was 1477 studies. **Study Selection:** Reports of efficacy outcomes were limited to randomized, controlled trials. Twenty-four trials involving more than 6600 patients, phase II studies that reported on withdrawals from therapy (the most reliable indicator of adverse effects), and all studies reporting on quality of life were abstracted. **Data Extraction:** Two independent reviewers abstracted each article by following a prospectively designed protocol. The meta-analysis combined data on 2-year overall survival by using a random-effects model and; reported results as a hazard ratio relative to orchiectomy. **Data Synthesis:** Ten trials of LHRH agonists involving 1908 patients reported no significant difference in overall survival. The hazard ratio showed LHRH agonists to be essentially equivalent to orchiectomy (hazard ratio, 1.1262 [corrected] [95% CI, 0.915 to 1.386]). There was no evidence of difference in overall survival among the LHRH agonists, although CIs were wider for leuprolide (hazard ratio, 1.0994 [CI, 0.207 to 5.835]) and buserelin (hazard ratio, 1.1315 [CI, 0.533 to 2.404]) than for goserelin (hazard ratio, 1.1172 [CI, 0.898 to 1.390]). Evidence from 8 trials involving 2717 patients suggests that nonsteroidal antiandrogens were associated with lower overall survival. The CI for the hazard ratio approached statistical significance (hazard ratio, 1.2158 [CI, 0.988 to 1.496]). Treatment withdrawals were less frequent with LHRH agonists (0% to 4%) than with nonsteroidal antiandrogens (4% to 10%). **Conclusions:** Survival after therapy with an LHRH agonist was equivalent to that after orchiectomy. No evidence shows a difference in effectiveness among the LHRH agonists. Survival rates may be somewhat lower if a nonsteroidal antiandrogen is used as monotherapy.

Additional systematic reviews summarize the literature supporting the use of androgen deprivation therapy for the treatment of metastatic prostate cancer.


**Recommendations**

The reviewers recommend the incorporation of metastatic prostate cancer treatment options into the WHO Model List of Essential Medicines, and recommend specifically that leuprolide (as a class agent with other LHRH agonists), bicalutamide, and diethylstilbestrol be added to the core Essential Medicines List.

**Additions proposed for Section 8.2 of the EML**

Leuprolide (to be added as a class agent to include other LHRH agonists)
Bicalutamide
Diethylstilbestrol (DES)
References

METASTATIC PROSTATE CANCER
Union for International Cancer Control
2014 Review of Cancer Medicines on the WHO List of Essential Medicines


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