Treatment options for recurrent prostate cancer

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The Urology Group
Prostate Cancer Support Group
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Reston Hospital
Treatment options for recurrent prostate cancer

- Background
- Radiation
- Hormone treatment
- Chemotherapy
- New agents
Treatment options for recurrent prostate cancer

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- Radiation
- Hormone treatment
- Chemotherapy
- New agents
Background

- Prostate cancer is the most commonly diagnosed solid organ cancer in the United States
  - 240,000 in 2012

- Prostate cancer is the second leading cause of cancer deaths among American men
  - 28,000 in 2012
Yesterday and today

1975
- 94 new cases per 100,000 men
- 31 deaths per 100,000 men
- 1986 FDA approves PSA
  - Increase in diagnosis
  - 1992: peaked at 237 cases per 100,000 men

2007
- 116 cases per 100,000 men
- 24 deaths per 100,000 men
- 90% of cancers diagnosed at early stage
PSA came into use 1980s – increased incidence of prostate cancer

www.cancer.gov/researchandfunding/snapshots/prostate
## Treatment localized cancer

<table>
<thead>
<tr>
<th>Year</th>
<th>Surgery</th>
<th>Radiation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1975</td>
<td>Open prostatectomy</td>
<td>External beams</td>
</tr>
<tr>
<td>2007</td>
<td>Nerve-sparing prostatectomy</td>
<td>External beams</td>
</tr>
</tbody>
</table>
Hormone therapy

1975
- Removal of the testicles
- Estrogen
  - Diethylstilbestrol (DES)
- Cardiovascular side effects

2007
- 1985: Gonadotropin-releasing hormone agonists
  - leuprolide (Lupron), goserelin (Zoladex), triptorelin (Trelstar), histrelin (Vantas)
- 1997: Anti-androgens
  - bicalutamide (Casodex), flutamide (Eulexin), nilutamide (Nilandron)
- 2008: Gonadotropin-releasing hormone agonists
  - degarelix (Firmagon)
- Ketoconazole (Nizoral)

www.cancer.gov/cancertopics/factsheet/cancer-advances-in-focus/prostate
**Chemotherapy**

1975

- none

2007

- 2004: docetaxel (Taxotere)
- 2010: cabazitaxel (Jevtana)
- Men who no longer respond to docetaxel
Immunotherapy

1975

- none

2007

- 2010: sipuleucel T (Provenge) vaccine
Bone agents

1975
- none

2007
- Bisphosphonates
  - zolendronic acid (Reclast, Zometa), alendronate (Fosamax), ibandronate (Boniva) risedronate (Actonel)
- Selective estrogen receptor modulators
  - raloxifene (Evist) and toremifene (Fareston)
- Teriparatide (Forteo)
- RANK ligand inhibitor
  - denosumab (Xgeva, Prolia)
- Calcitonin
Radiation to bone

1975
- none

2013
- Injectable radiation
- Radium-223 dichloride (Xofigo)
Prevention

1975

- none

2007

- 2003: finasteride (Proscar) decreases risk of prostate cancer 25%
- 2010: dutasteride (Avodart) decreases risk of prostate cancer in high risk men

www.cancer.gov/cancertopics/factsheet/cancer-advances-in-focus/prostate
The most common treatment for prostate cancer is surgery
   • Radical prostatectomy

In 2/3 of men, prostatectomy cures prostate cancer

In 1/3 of men, prostate cancer will come back within 10 years
Why does it come back?

- A microscopic amount of cancer cells left behind at surgery
- Spread of cancer outside the pelvis (low belly)
Risks for recurrent cancer

- Worrisome pathology after surgery
  - Positive margins – cancer seen at edge of removed prostate
  - Cancer in the glands behind the prostate (seminal vesicles)
  - Cancer bulging outside the capsule of the prostate
  - Higher Gleason score
Treatment options for recurrent prostate cancer

- Background
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- Chemotherapy
- New agents
New guidelines for radiation after surgery

- Radiation after Prostatectomy Panel
  - American Urological Association Education and Research, Inc. (AUA)
  - American Society for Radiation Oncology (ASTRO)
- Panel created in 2011
- Guidelines approved in 2013
American Urological Association (AUA) Guideline

ADJUVANT AND SALVAGE RADIOTHERAPY AFTER PROSTATECTOMY: ASTRO/AUA GUIDELINE

Ian Murchie Thompson,* Richard Valicenti,* Peter C. Albertsen, Brian Davis, S. Larry Goldenberg, Carol A. Hahn, Eric A. Klein, Jeff Michalski, Mack Roach III, Oliver Sartor, J. Stuart Wolf Jr. and Martha M. Faraday

Approved by the AUA Board of Directors
April 2013
How can you tell when cancer has come back?

- Check PSA blood test regularly after surgery
- Rising PSA after surgery means a higher risk of:
  - Spread of prostate cancer throughout the body (metastasis)
  - Death from prostate cancer

Clinical Principle

What PSA level indicates cancer has come back?

- Detectable or rising PSA value after surgery $\geq 0.2$ ng/ml
- Second test that confirms PSA $\geq 0.2$ ng/ml

Recommendation; Evidence Strength: Grade C

Guideline Statement 5. Radiation after Prostatectomy: ASTRO/AUA Guideline
Do I need any more tests?

- Restaging evaluation may be considered
  - Bone scan
  - CT scan of the pelvis (low belly)

- Option; Evidence Strength: Grade C

Radiation should be offered to men with PSA recurrence after surgery if there is no evidence of distant spread of cancer (scans show prostate cancer, bone pain).

**Recommendation; Evidence Strength: Grade C**

When should I get radiation?

- Radiation for PSA recurrence is most effective when given at lower levels of PSA

- **Clinical Principle**

What are the benefits of radiation?

- Potential benefits of controlling recurrent prostate cancer

What are the risks of radiation?

- **Short-term and long-term side effects**
  - Urinary: urinary frequency and urgency, blood in the urine, scar tissue in the bladder tube
  - Bowel: bowel frequency and urgency, diarrhea, blood in the stool
  - Sexual: erectile dysfunction

- **Clinical Principle**

Treatment options for recurrent prostate cancer

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- New agents
Hormone (androgen deprivation) therapy

- Hormone therapy is also called *androgen deprivation therapy* (ADT) or *androgen suppression therapy*

- The goal is to reduce levels of male hormones, called *androgens*, in the body, or to prevent them from reaching prostate cancer cells
The main androgens in men’s blood is testosterone and dihydrotestosterone (DHT).

85-90% is made in the testicles. 10-15% is made by the adrenal glands and other parts of the body.
Hormone (androgen deprivation) therapy

- Androgens stimulate prostate cancer cells to grow.
- Lowering androgen levels or stopping them from getting into prostate cancer cells makes prostate cancers shrink or grow more slowly.
- Hormone therapy alone does not cure prostate cancer.
- Eventually hormone therapy stops working.

www.cancer.org/cancer/prostatecancer/detailedguide/prostate-cancer-treating-hormone-therapy
Treatments to lower androgen levels

- Orchietomy (surgical castration)
- Luteinizing hormone-releasing hormone (LHRH) analogs
  - Similar to LHRH
- Luteinizing hormone-releasing hormone (LHRH) antagonists
  - Block LHRH
Orchiectomy (surgical castration)

- Surgical removal of the testicles
- Outpatient surgery
- Simple, least expensive
- Permanent
- Testicle prostheses available
- The brain sends chemical signals (LHRH/GnRH) to the pituitary gland
- The pituitary gland sends chemical signals (LH) to the testicles to make testosterone
- When testosterone is detected, these signals shut off
LHRH agonists suppress the pituitary gland’s call for testosterone

- Injection in the muscle every 3 to 6 months
- Testosterone flare - bone pain, block ureter, spinal cord compression

- leuprolide (Lupron, Viadur, Eligard)
- histrelin (Vantas)
- goserelin (Zoladex)
- triptorelin (Trelstar)
LHRH antagonists stop the production of testosterone in the testes and adrenal glands

Injection into skin (belly) every 28 days

No testosterone flare

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degarelix (Firmagon)

abarelix (Plenaxis)

Withdrawn from US 2005, used in Germany

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www.cancer.gov/cancertopics/understandingcancer/targetedtherapies/prostatecancer_htmlcourse/page2
Drugs that stop androgens from working

- **Anti-androgens**
  - casodex (bicalutamide), nilandron (nilutamide), eulexin (flutamide)

- **Androgen synthesis inhibitors** ("super-antiandrogens")
  - Abiraterone (Zytiga)

- **Next generation androgen receptor blockers**
  - Enzalutamide (Xtandi)
Blocks androgens from androgen receptor
- Oral pills taken daily
- Usually given before treatment with, or in combination with, an LHRH agonist

- casodex (bicalutamide)
- nilandron (nilutamide)
- eulexin (flutamide)
Other androgen-suppressing drugs

- Estrogens (female hormones)
  - Diethylstilbestrol (DES): cardiovascular side effects

- Ketoconazole (Nizoral)
  - Dramatically decreases testosterone level in 4 hours

- Aminogluthethimide (Cytadren)
  - Blocks steroid synthesis, including testosterone

www.cancer.org/cancer/prostatecancer/detailedguide/prostate-cancer-treating-hormone-therapy
Side effects of blocking testosterone

- Osteoporosis (bone thinning), broken bones
- Reduced or absent libido (sexual desire)
- Impotence (erectile dysfunction)
- Shrinking of testicles and penis
- Hot flashes, may get better or even go away with time
- Breast tenderness, growth of breast tissue
- Anemia (low red blood cell counts)
- Decreased mental sharpness
- Loss of muscle mass
- Weight gain
- Fatigue
- Increased cholesterol, possible cardiovascular problems (heart attack, death)
- Depression

www.cancer.org/cancer/prostatecancer/detailedguide/prostate-cancer-treating-hormone-therapy
Prevention

- Calcium and vitamin D
- Regular, weight-bearing exercise
- Bone density scans
When cancer no longer responds to hormone therapy

- Prostate cancer spreads throughout the body
- Historically, average survival was less than 2 years
- New treatments, longer survival
- Remains an incurable disease
Treatment options for recurrent prostate cancer

- Background
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- Chemotherapy
- New agents
Chemotherapy for prostate cancer

- For metastatic cancer (spread beyond the prostate), no longer responsive to hormone therapy
- Kill cancer cells or prevent them from multiplying
- Given through the vein (intravenous) or by mouth
Chemotherapy

- doxetaxel (Taxotere): intravenous, with other drugs
- cabazitaxel (Jevtana): injectable, with prednisone, if no response to docetaxel. Approved 2010
- mitoxantrone (Novantrone): with steroids, treats pain in advanced cancer
- estramustine (Emcyt): orally, sometimes with other drugs
- paclitaxel (Taxol): intravenous
- etoposide (Vepsid, V-16): intravenous and by mouth, combined with other drugs
- doxorubicin (Adriamycin): intravenous, an antibiotic. Risk of heart damage.
- vinblastine (Velban): intravenous, often with other drugs
docetaxel (Taxotere)

- One of the main types of chemotherapy to treat hormone-refractory prostate cancer
- Prevents cell growth
  - Inhibits microtubule assembly and disassembly
Mitosis (cell division) in normal cells
**docetaxel (Taxotere)**

- **Effectiveness:**
  - 17.5 month survival compared to 15.6 months with mitoxantrone chemotherapy
  - 18.9 month survival compared to 16.5 month survival with mitoxantrone

- **Side effects:** 26% had serious side effects
  - 11% stopped treatment

SWOG 9916; TAX-327
Severe adverse effects in patients undergoing treatment with docetaxel (n=2045)

- Neuromotor
- Hypersensitivity reactions
- Neurosensory
- Skin
- Stomatitis
- Asthenia
- Infections
- Fluid retention

Incidence (% patients)
Treatment options for recurrent prostate cancer

- Background
- Radiation
- Hormone treatment
- Chemotherapy
- New agents
New agents

- Immunotherapy
  - Sipuleucel-T (Provenge)

- Androgen blockers
  - abiraterone (Zytiga)
  - enzalutamide (Xtandi)

- Injectable radiation
  - Radium-223 dichloride (Xofigo)
sipuleucel-T (Provenge)
sipuleucel-T (Provenge)

- Immunotherapy
- Approved by FDA 2010
- First and only cancer vaccine ever approved by the FDA

IMPACT trial 2008
sipuleucel-T (Provenge)

- Autologous cellular immunotherapy,
  - Uses a man’s own immune cells (autologous) to battle prostate cancer

- Series of carefully orchestrated steps to make a drug that is personalized for each patient
sipuleucel-T (Provenge)

- Other therapies work against the body
  - Hormone therapy stops production of hormones
  - Chemotherapy therapy are toxic and focus on killing cancer cells
- Provenge is an approach that makes use of the body’s own immune cells (dendritic or T cells) which have been activated in a lab so they can recognize and battle prostate cancer cells
sipuleucel-T (Provenge)
Who can take sipuleucel-T (Provenge)?

- No or few symptoms: no cancer pain or, pain does not require narcotic pain medicine
- Cancer has spread to other areas in the body, such as bone (metastatic)
- Cancer has worsened despite hormone treatment (androgen resistant)
- Lower amount of cancer, healthy immune system

[www.prostate.net/2012/prostate-cancer/provenge/](http://www.prostate.net/2012/prostate-cancer/provenge/)
The National Comprehensive Care Network
How sipuleucel-T (Provenge) is prepared

- **Leukopharesis**: blood drawn through a large vein, goes into a machine where immune cells (dendritic or T cells), clotting proteins (platelets) and red blood cells are extracted. 3-4 hours

- Cells sent to a lab where the are activated to prompt the immune cells to look for and attack prostate cancer cells. 2-3 days

- Activated immune cells (personalized drug) is infused 3 days later. 2 hours

- 3 doses total. Treatment period: 5 weeks
sipuleucel-T (Provenge)

DAY 1
LEUKAPHeresis

Apheresis Center

DAY 2 - 3
SIPULEUCEL-T IS MANUFACTURED

Dendreon

DAY 3 - 4
PATIENT IS INFUSED

Doctor’s Office

COMPLETE COURSE OF THERAPY:
3 CYCLES
The blood of the cancer patient is collected and enriched to increase the population of immune cells (dendritic or T cells)
These cells are then grown in the laboratory in the presence of a protein or part of a protein that is present in or on the patient's tumor cells.
When the dendritic cells are put back into the patient, they signal the body’s own immune system to destroy all cells with the telltale protein, including cancer cells.
sipuleucel-T (Provenge)

- <10% of patients show a response in symptoms, PSA or on xray
  - Don’t expect to see a response

- Side effects:
  - Common: back pain, chills, fatigue, fever, headache, joint ache, and nausea (15%)
  - Less common: stroke or severe infusion reactions: breathing problems, chills, dizziness, fatigue, fever, headache, high blood pressure, muscle ache, nausea, vomiting, and weakness (3.5%)
  - Less than 1.5% stopped treatment because of side effects

www.prostate.net/2012/prostate-cancer/provenge/
sipuleucel-T (Provenge)

- **Cost:** $93,000
  - $31,000 per infusion; $23,000 per month of life
  - Insurance may cover, ¼ patients have co-payment up to 22%

- **Effectiveness**
  - 512 patients
  - Median overall survival: 25.8 months compared to 21.7 months
  - 22% decrease risk of death
  - Median extended survival: 4.1 months
abiaterone (Zytiga)
abiaterone (Zytiga)

- For metastatic, androgen-resistant prostate cancer before or after chemotherapy
- Androgen synthesis inhibitor ("super anti-androgen")
- Blocks production of testosterone early on
  - Testes, adrenal glands and prostate cancer cells
- Drops testosterone lower than any other known treatment
  - Can work even once other forms of androgen blockage have stopped working
Blocks testosterone production from testes, adrenal glands and prostate cancer cells

Androgen synthesis inhibitors ("super-antiandrogens")

- abiraterone (Zytiga)
Androgen production

Stops enzymes (CYP17A) from working

Cholesterol → CYP11A → 
Pregnenolone

17α-hydroxylase → 
Progestrone

Corticosterone → 
Aldosterone

17α-hydroxylase → 
17OH Pregnenolone

CYP17A lyase → 
17OH Progesterone

CYP17A → 
DHEA

DHEA → Androstenedione → Testosterone → SRD5A 1,2 → DHT

DHT → MDV3100 → AR engagement

Stops enzymes (CYP17A) from working

abiaterone (Zytiga)
abiaterone (Zytiga)

- Oral pill that is taken daily with steroid (prednisone) twice daily
- Average treatment period: 8 months.
- Side effects: cough, diarrhea, fluid retention, heartbeat disorders, high blood pressure, hot flashes, joint swelling, low potassium levels, muscle aches, upper respiratory tract infection, upset stomach, urinary frequency, and urinary tract infection.
- Steroid: weakening of the immune system
  - More susceptible to infection

www.prostate.net/2012/prostate-cancer/xtandi-vs-zytiga-comparison/
abiaterone (Zytiga)

- **Cost**: $5,000 per month
  - Covered by Medicare and most insurance companies

- **Effectiveness**
  - 1,195 patients
  - Median overall survival 14.8 months compared with 10.9 months
  - Median extended survival: 3.9 months
enzalutamide (Xtandi)
enazalutamide (Xtandi)

- For metastatic, androgen-resistant prostate cancer after docetaxel chemotherapy
- Androgen receptor blocker, works at several different steps
- Binds androgen receptor 5-8 times stronger than first generation androgen blockers

NCCN Guidelines for Prostate Cancer
Enzalutamide (XTANDI) is a medication used to treat certain types of prostate cancer. It works by competitively inhibiting androgen binding to androgen receptors, which prevents the cancer cell from receiving signals that promote growth.

Key mechanisms of action include:
- Competitively inhibits androgen receptor nuclear translocation.
- Inhibits androgen receptor interaction with DNA.
- Induces cell death, decreases prostate cancer cell proliferation, and decreases tumor volume.

This medication is designed to halt the progression of prostate cancer by targeting the androgen receptor pathway.
Androgen receptor (AR)

AR after conformational change due to testosterone or bicalutamide binding

1. Enzalutamide inhibits AR–testosterone binding with higher affinity than bicalutamide
2. Enzalutamide receptor inhibition blocks the activational change induced by AR–testosterone binding
3. Enzalutamide inhibits AR–testosterone nuclear translocation and DNA transcription
4. Enzalutamide lacks partial AR agonist activity that occurs with bicalutamide resistance

Testosterone
Bicalutamide
(Enzalutamide) (Xtandi)
enzalutamide (Xtandi)

- Oral pill taken daily
- Average treatment period: 8 months
- Side effects: anxiety, back pain, bloody urine, diarrhea, dizziness, fatigue, headache, hot flashes, joint pain, muscle weakness, musculoskeletal pain, respiratory infections, sleep problems, spinal cord compression, tingling sensation, and tissue swelling, seizures (1%)
enazlutamide (Xtandi)

- **Cost:** $7,450 per month
  - Medicare and most insurance companies will likely cover but need to check with insurance

- **Effectiveness:**
  - 1,199 men
  - Median overall survival 18.4 months compared with 13.6 months
  - Median extended survival: 4.8 months
NOW APPROVED for the treatment of patients with metastatic castration-resistant prostate cancer (mCRPC) who have previously received docetaxel

18.4 MONTHS MEDIAN OVERALL SURVIVAL
VS 13.6 MONTHS WITH PLACEBO

AND...

- 37% reduction in risk of death (HR = 0.63 [95% CI: 0.53, 0.75])
- XTANDI can be taken with or without food
- Patients were allowed, but not required, to take glucocorticoids
- Oral, once-daily dosing
- The rate of grade 3 and higher adverse reactions with XTANDI was 47% vs placebo at 53%
- Seven patients (0.9%) out of 800 treated with XTANDI 160 mg once daily experienced a seizure. No seizures occurred in patients treated with placebo

AFFIRM: A phase 3, global, placebo-controlled, randomized study of patients with mCRPC who previously received docetaxel

Introducing oral, once-daily XTANDI (enzalutamide) capsules

Select Important Safety Information
The most common adverse drug reactions (≥ 5%) were asthenia/fatigue, back pain, diarrhea, arthralgia, hot flush, peripheral edema, musculoskeletal pain, headache, upper respiratory infection, muscular weakness, dizziness, insomnia, lower respiratory infection, spinal cord compression and cauda equina syndrome, hematuria, paresthesia, anxiety, and hypertension.

Please see Important Safety Information on page 13 and accompanying Full Prescribing Information.
Osteoporosis in men

- 7% white men, 5% African-American men, and 3% Hispanic men (Qaseem 2008)

- Risks: hormone therapy (androgen blockage), 65 and older, medications (steroids), not enough calcium, not enough exercise, smoking, excess alcohol, family history, thin

- 20% of men who are on hormone therapy for prostate cancer will experience a fracture within 5 years. (Adler 2011)
Bone therapy: bisphosphonates

- Slow the rate of bone loss and can also lead to an increase in bone density

- Alendronate (Fosamax), ibandronate (Boniva), risedronate (Actonel), and zoledronic acid (Reclast), FDA approved
  - Most orally daily, weekly or monthly
  - Ibandronate (Boniva) is typically given IV every 3 months.
  - Zoledronic acid (Reclast) is given intravenously yearly

- Effectiveness: 112 men, alendronate for 1 year: bone mineral density had increased in the hip by 2.3%, spine by 5.1%
Selective estrogen receptor modulator (SERM) medications

- Oppose the actions of estrogen in the body, slow bone thinning, and can cause some increase in bone thickness.

- Two SERMs prescribed for off-label use in men are raloxifene (Evist) and toremifene (Fareston)
Synthetic parathyroid hormone

- Teriparatide (Forteo) is a synthetic form of the natural parathyroid hormone FDA approved for use in men who have severe osteoporosis

- Forms new bone, increases both bone mineral density and bone strength, reduces the risk of fracture

- Once daily as a subcutaneous injection
Humanized monoclonal antibody and antiresorptive agent

- Denosumab (Prolia)
- Reducing the activity of a specific receptor activator: RANK (Receptor Activator of Nuclear factor kB) ligand inhibitor
- FDA approval for postmenopausal women with osteoporosis, used off-label for men on hormone therapy
- Increase bone density and decrease vertebral fractures in men on hormone therapy (Adler/Gill 2011)
- Injection given every six months
Calcitonin

- Naturally occurring hormone that helps regulate calcium levels and slows the rate of bone thinning

- Injection or nasal spray

- Rarely used
  - Possible increased risk of prostate, skin, bone cancer
Radium-223 dichloride (Xofigo)
Radium-223 dichloride (Xofigo)

- Approved by FDA May 15, 2013
- For symptomatic, metastatic, androgen-resistant prostate cancer that has spread to bones but not to other organs
- Delivers radiation to tumor in bone without much damage to surrounding tissues
- Injection monthly for 6 weeks
- Side effects: nausea, diarrhea, vomiting, swelling of arms or legs, low blood cell counts
Radium-223 dichloride (Xofigo)

- **Cost:** $69,000 for complete course
  - New, check with insurance for coverage

- **Effectiveness**
  - 809 men
  - Median overall survival: 14 months versus 11 months
  - Median extension in survival: 3 months

[www.prostate.net/2013/prostate-cancer/xofigo-compared-to-xtandi/](http://www.prostate.net/2013/prostate-cancer/xofigo-compared-to-xtandi/)
Guideline on hormone resistant prostate cancer

- The American Urological Association commissioned an independent group to conduct a review and analysis of the literature on therapies for hormone resistant prostate cancer.

- Literature reviewed from 1996 to 2013.

- 303 eligible studies included.
Castration-Resistant Prostate Cancer: AUA Guideline

Michael S. Cookson, Bruce J. Roth, Philipp Dahm, Christine Engstrom, Stephen J. Freedland, Maha Hussain, Daniel W. Lin, William T. Lowrance, Mohammad Hassan Murad, William K. Oh, David F. Penson and Adam S. Kibel
Prostate cancer deaths are typically due to prostate cancer that no longer responds to hormone treatment and has spread throughout the body.

Historically the average survival for men with this type of cancer was less than two years.

We now have a variety of new treatments and longer survival.

Remains an incurable disease.
Which treatment is right for me?

- Symptoms
- Spread of cancer throughout the body (metastasis)
- Performance status
- Previous chemotherapy
## Appendix A: ECOG Performance Status

<table>
<thead>
<tr>
<th>Grade</th>
<th>ECOG Performance Status*</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Fully active, able to carry on all pre-disease performance without restriction</td>
</tr>
<tr>
<td>1</td>
<td>Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work</td>
</tr>
<tr>
<td>2</td>
<td>Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours</td>
</tr>
<tr>
<td>3</td>
<td>Capable of only limited self-care, confined to bed or chair more than 50% of waking hours</td>
</tr>
<tr>
<td>4</td>
<td>Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair</td>
</tr>
<tr>
<td>5</td>
<td>Dead</td>
</tr>
</tbody>
</table>
5 Index patients

1. Asymptomatic non-metastatic CRPC

2. Asymptomatic or minimally-symptomatic, mCRPC without prior docetaxel chemotherapy

3. Symptomatic, mCRPC with good performance status and no prior docetaxel chemotherapy

4. Symptomatic, mCRPC with poor performance status and no prior docetaxel chemotherapy

5. Symptomatic, mCRPC with good performance status and prior docetaxel chemotherapy

6. Symptomatic, mCRPC with poor performance status and prior docetaxel chemotherapy
**Staging/H&P/Imaging Algorithm**

**Non-metastatic CRPC**
- Clinicians should recommend observation with continued androgen deprivation.
- Clinicians may offer treatment with first-generation anti-androgens (flutamide, bicalutamide, and nilutamide) or first-generation androgen synthesis inhibitors (ketocapazole + steroidal) to select patients unwilling to accept observation.

**Index Patient 1**
- Clinicians should NOT offer systemic chemotherapy or immunotherapy outside the context of a clinical trial.

**Guideline Statements on Bone Health for all Index Patients**
- Clinicians should offer preventative treatment (e.g. supplemental calcium, Vitamin D) for fractures and skeletal related events to CRPC patients.
- Clinicians may choose either denosumab or zoledronic acid when selecting a preventative treatment for skeletal related events for CRPC patients with bony metastases.

**Index Patient 3**
- Clinicians should offer docetaxel.
- Clinicians may offer abiraterone + prednisone.
- Clinicians may offer ketoconazole + steroid, mitoxantrone or radionuclide therapy to patients who do not want or cannot have one of the previously listed treatments.
- Clinicians should NOT offer treatment with either estramustine or sipuleucel-T.

**Index Patient 4**
- Clinicians may offer treatment with abiraterone + prednisone.
- Clinicians may offer treatment with ketoconazole + steroid or radionuclide therapy to patients who are unable or unwilling to receive abiraterone + prednisone.
- Clinicians may offer docetaxel or mitoxantrone chemotherapy in select cases, specifically when performance status is directly related to the cancer.
- Clinicians should NOT offer sipuleucel-T.

**Index Patient 2**
- Asymptomatic or mildly symptomatic.
- Index Patient 2.
  - Clinicians should offer abiraterone + prednisone, docetaxel, systemic chemotherapy or sipuleucel-T immunotherapy.
  - Clinicians may offer first-generation androgen therapy, ketoconazole + steroid or observation to patients who do not want or cannot have one of the previously listed standard treatments.

**Index Patient 5**
- Good performance status.
  - Clinicians should offer treatment with abiraterone + prednisone, cabazitaxel or enzalutamide; if the patient received abiraterone + prednisone prior to docetaxel chemotherapy, cabazitaxel or enzalutamide should be offered.
  - Clinicians may offer ketoconazole + steroid if one of the previously listed standard treatments is unavailable.
  - Clinicians may offer retreatment with docetaxel to patients who were benefiting at the time of discontinuation (due to reversible side effects) of docetaxel chemotherapy.

**Index Patient 6**
- Poor performance status.
  - Clinicians should offer palliative care.
  - Clinicians may offer treatment with abiraterone + prednisone, enzalutamide, ketoconazole + steroid or radionuclide therapy.
  - Clinicians should NOT offer systemic chemotherapy or immunotherapy.
References


