Treatment Protocols

Treatment protocols for prostate cancer are provided below, including general treatment recommendations and those for localized prostate cancer, for recurrent disease, and for advanced or metastatic disease.

General treatment recommendations for prostate cancer

Selecting initial treatment requires assessing the risk of the disease spreading or progressing, which is based on evaluating life expectancy, comorbidities, biopsy grade (Gleason score), clinical stage, and prostate-specific antigen (PSA) levels of patients.

Treatment recommendations for clinically localized prostate cancer

Very low risk of recurrence:

- Patients with clinical stage T1c, Gleason score ≤6, PSA < 10ng/mL, fewer than 3 positive prostate cores, ≤50% cancer in each core, and PSA density < 0.15ng/mL/g, with a life expectancy < 20y, should be treated with active surveillance; they should also be referred for observation
- Surveillance includes periodic PSA, prostate exam, and prostate biopsy
- Optimal protocol for surveillance is still unknown: PSA as often as every 3mo or at least every 6mo; digital rectal examination (DRE) as often as every 6mo but at least every 12mo; repeat biopsy within 18mo but as often as every 12mo or if PSA and DRE change
- For treatment recommendations for patients with a life expectancy ≥20y, see initial therapy for Low Risk of Recurrence, below

Low risk of recurrence:

- Treatment for patients with clinical stage T1-T2a, Gleason score 2-6, PSA < 10 ng/mL, with a life expectancy < 10y, includes active surveillance
- Treatment for patients with a life expectancy ≥10y includes active surveillance OR
- Radical prostatectomy (RP) with or without pelvic lymph node dissection (PLND) if predicted probability of lymph node metastases ≥2%; RP is the standard therapy for localized prostate cancer, involving the removal of the prostate and seminal vesicles with or without pelvic lymph nodes; this may be done using either open or laparoscopic (robotic-assisted) technique OR
- Radiation therapy is a standard therapy for patients with localized disease, and 3-dimensional (3D) techniques such as 3D conformal radiation treatment (3D-CRT), which offer benefits such as reduced toxicity and the use of higher doses; second-generation techniques, including intensity-modulated radiation therapy (IMRT), are also required, especially if doses ≥78Gy are administered
- Radiation therapy doses of 75.6-79Gy in conventional 36-41 fractions to the prostate with 3D-CRT/IMRT with daily image-guided radiotherapy (IGRT) or brachytherapy (recommended dose rate: 145Gy for iodine-125 and 125Gy for palladium-103): A study by Haverkort et al found that position verification using gold markers and reduced planning target volume margins yielded adequate treatment of the prostate and a lower rectal wall dose in patients treated with curative external beam radiotherapy
- Patients with low-risk cancer are not candidates for pelvic lymph node irradiation or androgen deprivation
therapy (ADT)[11]

Intermediate risk of recurrence:

- Treatment for patients with clinical stage T2b-T2c, Gleason score 7, PSA 10-20 ng/mL, who have a life expectancy < 10y, include active surveillance **OR**
- Radiation therapy (doses of 78-80+ Gy) with 3D-CRT/IMRT with daily IGRT with or without short-term neoadjuvant/concomitant/adjuvant ADT for 4-6mo with or without brachytherapy (recommended dose rate: 145Gy for iodine-125 and 125Gy for palladium-103)[12, 13]
- Treatment recommendations for patients with a life expectancy ≥10y includes RP with PLND if predicted probability of lymph node metastasis ≥2% **OR**
- Radiation therapy (doses of 78-80+ Gy) with 3D-CRT/IMRT with daily IGRT with or without short-term neoadjuvant/concomitant/adjuvant ADT for 4-6mo with or without brachytherapy (recommended dose rate: 145Gy for iodine-125 and 125Gy for palladium-103)
- Intermediate-risk cancers consider combining brachytherapy (recommended dose rate: 145Gy for iodine-125 and 125Gy for palladium-103) with EBRT (40-50Gy) with or without 4-6mo neoadjuvant/concomitant/adjuvant ADT
- Administering ADT before, during, and after radiation prolongs survival in patients

High risk of recurrence:

- Clinical stage T3a, Gleason score 8-10, PSA >20 ng/mL
- Treatment options include radiation therapy (doses of 78-80+ Gy) with 3D-CRT/IMRT plus long-term neoadjuvant/concomitant/adjuvant ADT for 2-3y **OR**
- Radiation therapy (doses of 78-80+ Gy) with 3D-CRT/IMRT with daily IGRT plus brachytherapy (recommended dose rate: 145Gy for iodine-125 and 125Gy for palladium-103) with or without short-term neoadjuvant/concomitant/adjuvant ADT for 4-6mo **OR**
- RP plus PLND for selected patients with no fixation
- High-risk cancers may be treated with combination EBRT (40-50Gy) and brachytherapy with or without 4-6mo neoadjuvant/concomitant/adjuvant ADT

Alternative treatment recommendations for localized prostate cancer

Other treatments that have been used in the initial management of localized prostate cancer include cryotherapy, high-intensity focused ultrasound, and ablation therapy.

Cryotherapy:

- Cryotherapy is also known as cryosurgery or cryoablation, and it involves using transrectal ultrasonographic guidance; percutaneous cryoprobes are placed and used to freeze the prostate
- This treatment is not optimal but may be used in select patients with localized prostate cancer or as focal therapy in low-risk patients (experimental)[14]
- Can also be considered as salvage therapy after failed radiation therapy[15]
- Complications include tissue sloughing, perineal ecchymosis, stricture or contracture, incontinence, impotence, and fistula formation between the urinary and gastrointestinal tracts

High-intensity focused ultrasound:

- Acoustic ablative technique that uses ultrasound to destroy prostate tissue
- Not yet FDA approved in the US, pending multicenter trials

Particle beam therapy:

- Similar to radiation therapy but uses protons for energy; however, it lacks long-term follow-up

Biochemical failure

- Approximately 50% of patients treated with intent for cure will have biochemical recurrence; most commonly presents with a rising PSA level[16]
- Biopsy of the prostatic bed is usually not recommended unless the patient is a candidate for salvage therapy

Post–radical prostatectomy recurrence

- Defined as a detectable PSA that increases on 2 subsequent measurements or a PSA that fails to fall to
undetectable levels

- Best PSA threshold unknown but probably between 0.2 and 0.4\[17\]
- Treatment options include salvage radiation therapy, androgen deprivation, and surveillance
- Adjuvant radiation therapy may be more beneficial than salvage radiation therapy in men with poor pathologic features\[2, 3\]

Post–radiation therapy recurrence

- Defined as a rise in PSA of 2ng/ml or more above the nadir\[18, 19, 20\]
- PSA can bounce up and down after radiation
- Treatment options include salvage prostatectomy, androgen deprivation, surveillance, high-intensity focused ultrasound (HIFU) (trials), cryotherapy, re-irradiation

Treatment recommendations for locally advanced prostate cancer

**Very high risk:**

- Clinical stage T3b-T4 treatment options include radiation therapy (doses of 78-80+ Gy) with 3D-CRT/IMRT plus long-term neoadjuvant/concomitant/adjuvant androgen deprivation therapy (ADT) for 2-3y
- Radiation therapy (doses of 78-80+ Gy) with 3D-CRT/IMRT with daily IGRT plus brachytherapy with or without short-term neoadjuvant/concomitant/ADT for 4-6mo
- RP plus PLND for selected patients with no fixation
- ADT in selected patients

**Metastatic disease:**

- Any T, N1: Treatment includes ADT or radiation therapy (doses of 78-80+ Gy) with 3D-CRT/IMRT with IGRT plus long-term neoadjuvant/concomitant/adjuvant ADT for 2-3y
- Any T, any N, M1: Treatment includes only ADT for patients with M1

Androgen deprivation therapy (ADT) recommendations for advanced or metastatic disease

- ADT is the preferred initial treatment for symptomatic metastatic prostate cancer because androgenic effects promote the growth and malignant transformation of prostatic tissue\[21\]
- ADTs include luteinizing hormone ( LH) receptor agonists (eg, histrelin, leuprolide), gonadotropin-releasing hormone ( GnRH) receptor agonists (eg, goserelin, histrelin, leuprolide, triptorelin) and antagonists (eg, degarelix), and complete androgen blockade (CAB)
- CAB includes medical or surgical castration with an oral antiandrogen (eg, bicalutamide, flutamide, nilutamide)\[22\]
- Patients who do not show an adequate suppression of serum testosterone (< 50 ng/dL) may be considered for CAB
- Monotherapy of nonsteroidal antiandrogens are less effective but are associated with fewer hot flashes and fatigue and do not impair libido
- If hormone therapy fails, that therapy should be continued into and through the next hormone manipulation

Gonadotropin-releasing hormone agonists:

- Therapy with GnRH analogs may induce medical castration by suppressing LH production
- These agonists can potentially cause a transient surge of LH when therapy is initiated before the LH levels fall (flare phenomenon)
- GnRH agonists are offered in 1mo, 3mo, and once-yearly depots; it is necessary to premedicate with antiandrogen to prevent flare phenomenon
  - Leuprolide: 7.5 mg IM monthly or 22.5 mg IM every 3mo or 30 mg IM every 4mo or 45 mg IV every 6mo
  - Histrelin: one 50mg implant SC every 12mo\[23\]; continue therapy until disease progression
  - Goserelin: 3.6 mg implant SC monthly or a 10.8 mg implant\[23\] SC every 3mo
  - Triptorelin: 3.75 mg IM monthly or 11.25 mg IM every 3mo or 22.5 mg IM every 6mo

Gonadotropin-releasing hormone antagonists:
Pure GnRH antagonists suppress testosterone and avoid the flare phenomenon associated with GnRH agonists.

- **Degarelix**: 120 mg SC x 2 doses (ie, 2 separate injections totaling 240 mg), and then, after 28 days, begin monthly maintenance dose of 80mg SC

**Nonsteroidal antiandrogens:**

- Antiandrogens bind to androgen receptors and competitively inhibit their interaction with testosterone and dihydrotestosterone
- These agents do not decrease LH levels and androgen production
- Antiandrogens are usually combined with a GnRH agonist in order to prevent a disease flare caused by the transient increase in testosterone levels
- **Flutamide** 250 mg PO TID OR
- **Bicalutamide** 50 mg PO daily; patients refractory to other antiandrogen agents may start with 150 mg PO daily OR
- **Nilutamide** 300 mg PO daily for 30 days, and then 150 mg PO daily

**Hormone-refractory prostate cancer:**

- Taxanes alone or in combination with other agents have demonstrated efficacy in the treatment of hormone-refractory prostate cancer
- Recommended dose is **paclitaxel** 135 mg/m$^2$ IV as a 24h infusion on day 1; repeat every 21 days OR
- Paclitaxel 150 mg/m$^2$ IV as a 1 h infusion weekly for 6wk; repeat cycle every 8wk

**Management of castration-recurrent prostate cancer**

- All patients with metastatic disease become resistant to ADT
- The median time to symptomatic progression after a rise in PSA level of more than 4ng/mL is approximately 6-8mo, with a median time to death of 12-18mo
- Symptomatic patients have a median survival of 1y
- Radiation may be used for palliative reasons in patients with painful bone metastases or impending spinal cord compression
- Surgical intervention may be necessary for weight-bearing bones involved in pathologic fracture
- Therapeutic options are limited, and the focus is on improving quality of life using single or multimodal therapies
- **Docetaxel** every 3wk plus prednisone is the treatment of choice for men with symptomatic castration-recurrent prostate cancer;\(^{[24, 25, 26]}\) recommended dose is **docetaxel** 75 mg/m$^2$ IV on day 1 plus prednisone 5 mg PO BID; repeat cycle every 21 days for up to a total of 10 cycles (premedicate with oral corticosteroids starting 1 day before docetaxel administration to reduce incidence of hypersensitivity reactions and fluid retention)
- Symptomatic men who are not candidates for docetaxel-based regimens may be candidates for **mitoxantrone** 12 mg/m$^2$ IV on day 1 plus prednisone 5 mg PO BID daily; repeat cycle every 21 days\(^{[24, 25, 26]}\)
- Men with less advanced disease, good performance status, life expectancy >6 mo, no visceral disease, and no or minimal symptoms and who are resistant to standard hormone treatment may be candidates for autologous immunotherapy with sipuleucel-T\(^{[27]}\)
- Sipuleucel-T requires 3 complete doses IV given at approximately 2 wk intervals (median dosing interval, 2 wk; range, 1-15 wk); infuse IV over 60 min; premedicate with oral acetaminophen and an antihistamine approximately 30min prior to administration\(^{[27, 28]}\)
- **Abiraterone** has been approved for the treatment of patients with metastatic castration-resistant prostate cancer who are either chemotherapy-naive or those who have had prior docetaxel therapy; recommended dose is 1000mg PO once daily plus prednisone 5mg PO BID\(^{[29, 30, 31, 32]}\)

**Treatment recommendations for late-stage castration-resistant prostate cancer with prior docetaxel chemotherapy\(^{[29, 30]}\):**

- Abiraterone has been approved for the treatment of patients with metastatic castration-resistant prostate cancer who are either chemotherapy-naive or those who have had prior docetaxel therapy; recommended dose is 1000 mg PO once daily plus prednisone 5 mg PO BID\(^{[29, 30, 31, 32]}\) a study by de Bono et al found that abiraterone acetate prolonged overall survival among patients with metastatic castration-resistant prostate cancer who had received chemotherapy prior to administration\(^{[33]}\)
- Alternative regimens include cabazitaxel with prednisone for patients who have hormone-refractory metastatic prostate cancer that was previously treated with a docetaxel-containing treatment regimen;
**cabazitaxel** 25 mg/m² IV every 3wk; infuse IV over 1h; use inline filter (0.22µm) during administration

**plus** prednisone 10 mg PO daily; reduce cabazitaxel dose to 20 mg/m² with prolonged or febrile neutropenia or with persistent or severe diarrhea

- **Enzalutamide** (160 mg PO daily) is an androgen receptor inhibitor that is indicated for metastatic castration-resistant prostate cancer in patients who have previously received docetaxel

**Treatment recommendations for patients with castration-recurrent prostate cancer and bone metastases**

- Bisphosphonates are recommended for all men with hormone-refractory prostate cancer and bone metastases[^34, 35]
- Bisphosphonates have been shown to reduce skeleton-related events such as pathologic fracture
- **Zoledronic acid** 4 mg IV annually over no less than 15min
  OR
- **Alendronate** 70 mg PO weekly
  OR
- **Denosumab** 120 mg SC every 4wk

The radiopharmaceutical, radium-223 dichloride (Xofigo), was approved in May 2013 for men with castration-resistant prostate cancer with symptomatic bone metastases and no known visceral metastatic disease.[^36]

- 50 kBq (1.36 microcurie) per kg IV infused over 1 minute; repeat q4wk for 6 cycles total; dosage calculation must be based on decay correction factor of radium-223 (listed in prescribing information)

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Disclosure: Nothing to disclose.

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Disclosure: Nothing to disclose.

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[^34]: 1.
[^35]: 2.
[^36]: 3.


