The three main criteria for initiation of radical treatment in patients showing disease progressions are:
- PSA-DT of less than 2 years,
- re-biopsy of primary tumour to Gleason grade 4 or more
- more than 50 per cent of positive cores showing cancer involvement.

(NICE Active Surveillance Protocol)

**Year 1**
- 3-month Prostate-Specific Antigen (PSA) check
- 6-month DRE
- 12-month re-biopsy
- Monitor PSA kinetics

**Year 2 - 4**
- 3 – 6 month PSA check
- 6 – 12 month DRE
- Monitor PSA kinetics

**Year 5 and beyond**
- 6-month PSA check
- 12-month DRE
- Monitor PSA kinetics

Does the patient wish to change to alternative treatment options? OR Is there evidence of disease or symptomatic progression?

- Yes: Consider alternative management/treatment strategies
- No: Patient consulted by Urologist and CNS to discuss appropriate treatment options and information given to include:
  - aims of treatment(s)
  - side effects
  - consent.

Considerations for alternative management strategies:
- personal preferences, comorbidities and life expectancy
- patient pathology and radiology
- biopsy and grade progression
- clinical progression.

Surgery External Beam Radiotherapy Brachytherapy Hormone therapy Watchful waiting
Watchful waiting

Consider for older men and those with medical co-morbidities with a shorter life-expectancy where benefit of radical treatment is unlikely/limited.

Recommended for **localised** and **locally advanced** prostate cancer (M0, N0/1). Suitable for men for whom curative treatment is not an option and are not symptomatic, or those who chose not to undergo treatment.

Begin watchful waiting

“**All men with prostate cancer should be given information and advice on likelihood and management of consequences of treatment and late effects, including red flag symptoms, even those men that opt for watchful waiting.**”

See **Support Pathway** (General side effect management principles).

GP management for symptoms and PSA monitoring with predefined monitoring agreed (or defined) by specialist including re-referral criteria.

Evidence of disease progression:
- rapidly rising PSA level
- bone pain.

Locally advanced disease (symptomatic or rapid PSA rise)

Urological MDT review

Androgen deprivation therapy to control symptoms

Localised disease (rapid PSA rise)

Urological MDT review

Consider how radical treatments may affect any existing comorbidities and life expectancy
Surgery – radical prostatectomy

What is the patient’s stage of disease?

Low risk (T1 – 2a): PSA < 10, Gleason 6, with few comorbidities

Active surveillance as optimal treatment unless patient chooses surgery.

Intermediate risk: (T2b): PSA 10 – 20, Gleason 7

Consultation with urologist and CNS, to include:
- treatment outcomes – T2c – 3a to be advised that there is a chance secondary treatment in the form of hormone therapy or radiotherapy may be required following surgery
- surgical approaches available
- side effects
- consent.

High risk / Locally advanced (T2c – T3b): Any PSA, Any Gleason ≥ 8, N1

Offer medical castration luteinising-hormone-releasing hormone (LHRH) agonist in combination with external beam radiotherapy as optimal treatment unless patient chooses surgery.

Gleason 4+3 or 4+4 with PSA > 20 – consider extended lymph node dissection

Pelvic lymph node dissection risks:
- lymph leak
- lymphocele formation
- nerve damage.

Suitable for surgery?

Yes

Consider other treatment options (e.g. external beam radiotherapy)

No

Pre-treatment seminar
Nurse led session to discuss:
- side effects
- implications of surgery
- catheter care
- continence and continence products
- pre-surgery baseline sexual function (erectile function)
- pelvic floor exercises / penile rehabilitation.

continues on next page
Preoperative Assessment (a/w protocols).
- High risk anaesthetic assessment.
- Assess baseline continence and erectile function.

**Post surgery**
- Early mobilisation, eating and drinking.
- Pain relief and anti-emetic medications.
- Catheter management.

**Stratified follow-up**
- 6 week post-op PSA test.
- Follow-up 6 – 8 weeks.
- PSA re-testing at 3 months and 6 months.
- Annual follow-up.

Follow up should include assessment of urinary incontinence and ED with appropriate support and treatment.

**PSA remains low or at 0?**
- No

**PSA remains persistent?**
- Yes

**PSA rises 3 times?**
- Yes

After at least 2 years, NICE guidance advises that for men with a stable PSA, who have had no significant treatment complications, follow-up can be offered outside of hospital by telephone or secure electronic communications (unless they are taking part in a clinical trial that requires formal clinic-based follow-up). Direct access to the urological cancer MDT should be offered and explained.

Try to locate the recurrent cancer and refer to Clinical Oncologist for local control with adjuvant radiotherapy.

Refer to Clinical Oncologist for salvage radical radiotherapy to the prostatic bed if they have +/- lymph nodes and no known metastases.

Patients with high volume nodal disease and multiple adverse tumour characteristics: early adjuvant hormone therapy.
External beam radiotherapy (EBRT)

Is the patient suitable for radiotherapy?

- Yes
  - Consultation with Oncologist and CNS, to include:
    - potential treatment outcomes
    - length of treatment and patient attendance
    - side effects
    - consent.
  - See Support Pathway for more information on pelvic radiotherapy side effects (section 3.4).

- No
  - Unsuitable for radiotherapy, explore alternative treatments for stage of disease (e.g. radical prostatectomy)

What is the patient’s stage of disease?

- Localised T1 – 3a, Gleason < 8, any PSA
  - Low or intermediate / high risk?
    - Low risk (T1 – 2a): hypo-fractionated high-dose IMRT
      - 60 gy in 20 fractions over 4 weeks
      - In case of recurrence, men exposed to 78 gy will not have the option of additional radiotherapy.
    - T2b and T2c – 3a: IMRT
      - 78 gy in 37 fractions over 7 – 8 weeks

- High-risk / locally advanced
  - Offer medical castration (luteinising-hormone-releasing hormone [LHRH] agonist) as androgen deprivation therapy, 6 months prior and for 1 – 3 years after. Include co-administration of an antiandrogen to LHRHa to prevent testosterone flare – 1 week before and 3 weeks after the first injection. Administer for 4 weeks.
  - External beam radiotherapy to a dose of 76 – 78 gy, which can be combined with brachytherapy (high-dose rate OR low dose rate). Radiotherapy should be given in combination with long-term androgen deprivation therapy (2 – 3 years).

- Patient struggling with side-effects of androgen deprivation therapy?
  - Intermittent treatment (strategy to minimise side effects of testosterone loss):
    - highly motivated patients with a major PSA response after induction period
    - stop – PSA level < 4 ng/ml after 6 – 7 months of treatment
    - resume – PSA level is > 10-20 ng/ml.


**External beam radiotherapy (EBRT) continued...**

On the day of treatment with Radiographer:
- fluid intake checked
- bladder scan to ensure full bladder
- check bowel activity / bowel preparation
- positioning (Radiographer).

Assessment prior to next fraction administered to check fitness and side effects.

**Is the patient medically fit enough to continue with radiotherapy?**

Are the side effects of treatment well controlled?

Does the patient wish to continue to the next fraction of radiotherapy?

Yes

Proceed to next fraction or complete treatment

No

Consultation with Oncologist to explore alternative treatment options or referral back to Urologist

**Mid-treatment review with Radiographer or CNS (weekly)**

PSA test one week before Oncology review

Post treatment consultation with Oncologist

**Is there a sign of biochemical recurrence?**

(2 – 3 years androgen deprivation therapy – PSA rise within this timeframe is likelihood of castrate resistance)

Yes

Definition of biochemical relapse: The 2005 ASTRO consensus definition (PSA greater than current nadir + 2 ng/ml; Roach, 2006), has a sensitivity of 74 per cent and specificity of 71 per cent for any clinical failure.

Staging investigation is undertaken to identify whether cancer is still present locally within the prostate or has metastasised.

Localised/locally advanced

No

Late effects can occur months to years after radiotherapy, may include: urinary problems (weak flow), bowel problems, erectile dysfunction, hip and bone pain/weakness. See Support Pathway (section 3.4).

Metastatic

Go directly to M1 pathway

Is the patient symptomatic?

Yes

For physically fit patients, radical prostatectomy can provide a curative salvage therapy for biochemical relapse after radiotherapy.

No

Monitor for symptoms

Late effects can occur months to years after radiotherapy, may include: urinary problems (weak flow), bowel problems, erectile dysfunction, hip and bone pain/weakness. See Support Pathway (section 3.4).

**Short-term side effects (6 – 8 weeks)**

including: diarrhoea, rectal pain, unusual urinary frequency.
What is the patient’s stage of disease?

Low risk localised
PSA < 10 ng/ml and Gleason score ≤ 6, and clinical stage T1 – T2a

Intermediate risk localised
PSA 10 – 20 ng/ml, or Gleason score 7, or clinical stage T2b

High risk localised
PSA > 20 ng/ml, or Gleason score 8–10, or clinical stage ≥ T2c

Locally advanced
T3+, NX, N1

Is Gleason score 3+4?

Yes

Large prostate (> 75cc)? IPSS > 12? History of prostate outflow surgery? Poor urinary stream?

No

Unsuitable for brachytherapy, explore alternative treatments: active surveillance or external beam radiotherapy or surgery

Yes

High-dose rate / low-dose rate brachytherapy + external beam radiotherapy (boost or in combination)

Consider androgen deprivation therapy for up to 3 years for men with high-risk localised prostate cancer and discuss the benefits and risks of this option with them.

Is the prostate now adequately sized?

Yes

Same day

Start low-dose rate brachytherapy

No

Planning session in theatre; volume study – with estimate based on MRI.

Is the prostate less than 60cc?

No

Consider 3 – 6 months of hormone therapy to shrink prostate to acceptable size before proceeding to pre-operative assessment.

No

Do not offer brachytherapy alone to men with high-risk localised prostate cancer.

Yes

External beam radiotherapy + androgen deprivation therapy and / or high-dose rate OR low-dose rate. The brachytherapy boost is sometimes used to delay androgen deprivation therapy if Gleason 4+3, but androgen deprivation therapy should then be administered for up to 3 years.

See Support Pathway for more information on pelvic radiotherapy side effects (section 3.4).
Stratified follow-up
- Initial follow-up 4 – 6 weeks.
- PSA testing and subsequent follow-up (for men not on androgen deprivation therapy):
  - Year 1: every 3 months
  - Years 2 – 5: every 6 months
  - Years 6+: every 12 months
- Men on androgen deprivation therapy will have their PSA levels suppressed for up to 3 years
- Ensure effective short-term side-effect support.
- Ensure support for late-effects.

Is there a sign of biochemical recurrence?
(2 – 3 years androgen deprivation therapy – PSA rise within this timeframe is likelihood of castrate resistance)

Definition of biochemical relapse:
The 2005 ASTRO consensus definition (PSA greater than current nadir + 2 ng/ml: Roach, 2006), has a sensitivity of 74 per cent and specificity of 71 per cent for any clinical failure.

Staging investigation is undertaken to identify whether cancer is still present locally within the prostate or has metastasised.

Localised/locally advanced

Metastatic

Is the patient symptomatic?

Yes

For physically fit patients, radical prostatectomy can provide a curative salvage therapy for biochemical relapse after radiotherapy.

No

Monitor for symptoms

Late effects can occur months to years after radiotherapy, may include: urinary problems (weak flow), bowel problems, erectile dysfunction, hip and bone pain/weakness. Please see Support Pathway (section 3.4).

Go directly to M1 pathway

Continue to monitor with PSA measurements after 6 and 12 months
Hormone therapy (first line): locally advanced and metastatic prostate cancer

What is the patient’s stage of disease?

Locally advanced (N1 M0)

Offer medical castration (luteinising-hormone-releasing hormone [LHRH] agonist) as androgen deprivation therapy. Include co-administration of an anti androgen to LHRHa to prevent testosterone ‘flare’ – 1 week before and 3 weeks after the first injection. Administer for 4 weeks.

Metastatic prostate cancer (M1)

Offer medical or surgical castration (luteinising-hormone-releasing hormone [LHRH] agonist) as androgen deprivation therapy. Include co-administration of an anti androgen to LHRHa to prevent testosterone ‘flare’ – 1 week before and 3 weeks after the first injection. Administer for 4 weeks.

Consider radical prostatectomy (RP) with patients high-risk localised disease and a life expectancy of >10 years.

See Surgery Pathway

Consultation with Oncologist and CNS, to include:
- potential combination treatment outcomes
- length of treatment and patient attendance
- side effects
- consent.

What is the patient’s stage of disease?

Consider Degarelix for advanced hormone-dependent prostate cancer in patients with spinal metastases – no anti-androgen needed.

Intermittent treatment (strategy to minimise side effects of testosterone loss):
- highly motivated patients with a major PSA response after induction period
- stop – PSA level < 4 ng/ml after 6–7 months of treatment
- resume – PSA level is > 10-20 ng/ml.

Patient struggling with side-effects of androgen deprivation therapy?

Is the patient able to tolerate radical treatment?

No

Yes

Main side effect profile, mainly due to testosterone loss:
- hot flushes
- changes to sex life
- weight gain strength and muscle loss
- loss of body hair
- bone thinning
- mood changes
- risk of heart disease, stroke and diabetes.

Please see Support Pathway (section 3.6).

continues on next page
Hormone therapy (first line): locally advanced and metastatic prostate cancer continued...

Locally advanced (N1 M0)

Combine medical castration with radical radiotherapy (EBRT) – NICE Guidelines 2014

External beam radiotherapy to a dose of 76–78 Gy, combined with brachytherapy (high or low-dose rate). Radiotherapy should be given in combination with long-term androgen deprivation therapy (2 – 3 years).

Consultation with Oncologist to explore alternative treatment options including abiraterone (if metastatic) and enzalutamide.

High-Risk Locally Advanced (At least two of: T3/4 disease, Gleason score of 8–10, and prostate-specific antigen 40 ng/ml)

Is the patient suitable for chemotherapy and able to make an informed choice about it as an option?

Yes

Continue medical castration (ADT) combined with chemotherapy (docetaxel – 6 cycles) to all patients whose first presentation is M1 disease. Select patients with high-risk MO disease may be offered chemotherapy where it is expected to improve their cancer outcomes.

Metastatic prostate cancer (M1)

Newly diagnosed M1 with 12 weeks androgen deprivation therapy?

Yes

Is the patient suitable for chemotherapy?

Yes

Continue medical castration to patients unfit for, or unwilling to consider, castration combined with chemotherapy. Where possible consider offering abiraterone acetate (1000mg od) plus prednisolone (5mg od) in addition to castration.

No

Has the patient's cancer progressed?

Yes

Definition of biochemical relapse: The 2005 ASTRO consensus definition (PSA greater than current nadir + 2 ng/ml: Roach, 2006), has a sensitivity of 74 per cent and specificity of 71 per cent for any clinical failure.

Has the patient's cancer progressed?

No

Continue to monitor with PSA measurements after 6 and 12 months

Yes

In patients with measurable disease, progression is a rising PSA after 3 years or the appearance of new soft tissue metastases or a clear increase in size of existing metastases (usually at least a 20 per cent increase in size). If bone metastases = at least 2 new metastases on a bone scan confirmed by appearance of at least 2 more on another scan performed at least 6 weeks later.
Hormone therapy (second line)

What is the patient’s stage of disease?

TanyN1MO: Rising PSA levels in the absence of metastases or symptoms and despite androgen-deprivation therapy

High-Risk Locally Advanced (At least two of: T3/4 disease, Gleason score of 8–10, and prostate-specific antigen ≥ 40 ng/ml)

Metastatic (TanyNaryM1a-c)

Has the patient’s cancer progressed?

No

Initial = rising PSA or the appearance of new metastases with castrate levels of testosterone

Yes

Continue to monitor for disease progression

Palliative care, which can include radiotherapy

For patients with non-metastatic progression: Combined Anti-Androgen Blockage (CAB)

Bone scan to rule out the presence of metastases or micrometastases.

External beam radiotherapy (if not previously received) and consider high or low-dose rate brachytherapy in combination.

See External beam radiotherapy Pathway

For patients with metastatic disease: The following treatment options are based on the patient’s preferences and contra-indications, as well as clinical expertise and prior treatments received. There is little evidence available for treatments sequencing. The patient should continue to be monitored for disease progression.

Consider the following:

- Docetaxel (rechallenged if patient has responded well) – Up to 10 cycles if treatment is effective and side effects tolerated
- Dexamethasone (low-dose dexamethasone therapy is thought to be effective in addition to second- or third-line anti-androgens, or anti-androgen withdrawal)
- Prednisolone (often in combination with docetaxel and cabazitaxel to lower prostate-specific antigen and quality-of-life benefits, including appetite stimulation)
- Abiraterone or Enzalutamide
- Radium 223 (if the patient has symptomatic bone metastases and no known visceral metastases, have had docetaxel and/or is contra-indicated to docetaxel)
- Cabazitaxel (in combination with prednisolone if the patient has had docetaxel).

Is the patient no longer responding to treatment and experiencing disease progression?

No

Yes

If the patient has visceral metastases and no symptomatic bone metastases see Support Pathway (section 3.8).
Chemotherapy

What is the patient’s stage of disease?

High-Risk Locally Advanced (At least two of: T3/4 disease, Gleason score of 8–10, and prostate-specific antigen 40 ng/ml).

Is the patient suitable for chemotherapy?

Metastatic (TanyNanyM1a-c)

Is the patient suitable for chemotherapy and able to make an informed choice about it as an option?

All patients

Go to External Beam Radiotherapy Pathway and follow for locally advanced prostate cancer. For all stages continue castration therapy for up to 3 years total (in the absence of disease progression).

Offer medical castration (androgen deprivation therapy) combined with chemotherapy (docetaxel – 6 cycles) to all patients whose first presentation is M1 disease. Select patients with high-risk MO disease may be offered chemotherapy where it is expected to improve their cancer outcomes.

Offer medical castration to patients unfit for, or unwilling to consider, castration combined with chemotherapy. Where possible consider offering abiraterone acetate (1000mg od) plus prednisolone (5mg od) in addition to castration.


Has the patient’s cancer progressed?

No

Optimal treatment.

Yes

Initial = rising PSA or the appearance of new metastases with castrate levels of testosterone.

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For patients with metastatic disease: The following treatment options are based on the patient’s preferences and contra-indications, as well as clinical expertise and prior treatments received. There is little evidence available for treatments sequencing. The patient should continue to be monitored for disease progression.

Consider the following:
- Docetaxel (rechallenged if patient has responded well) – Up to 10 cycles if treatment is effective and side effects tolerated
- Dexamethasone (low-dose dexamethasone therapy is thought to be effective in addition to second- or third-line anti-androgens, or anti-androgen withdrawal)
- Prednisolone (often in combination with docetaxel and cabazitaxel to lower prostate-specific antigen and quality-of-life benefits, including appetite stimulation)
- Abiraterone or Enzalutamide
- Radium 223 (if the patient has symptomatic bone metastases and no known visceral metastases, have had docetaxel and/or is contra-indicated to docetaxel)
- Cabazitaxel (in combination with prednisolone if the patient has had docetaxel).

Is the patient no longer responding to treatment and experiencing disease progression?

No
- Continue to monitor for disease progression

Yes
- Palliative care, which can include radiotherapy