Prostate Cancer UK’s Best Practice Pathway

TREATMENT
Active surveillance

What level of risk is the patient’s prostate cancer?

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

Offer active surveillance

Consider active surveillance

Is Gleason Score ≤ 3+4 and mpMRI T stage ≤ T2 and Biopsy and MRI are concordant and PSA density ≤ 0.2 ng/ml

Yes

Begin active surveillance

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

No

Not suitable for active surveillance

Offer multiparametric MRI (mpMRI) to people having active surveillance who have not had an mpMRI previously. If the mpMRI results do not agree with the biopsy findings, discuss at MDT with the potential to offer a new MRI-targeted biopsy (NICE Active Surveillance Protocol)

Optimal treatment option for low risk localised disease

Prostate Cancer UK active surveillance consensus

Year 1

- Provide a personalised plan to primary care that includes: details of PSA test interval, individualised PSA threshold for re-assessment and follow-up (The factors that will influence PSA interval could include: PSA history; mpMRI results; and PSA density)
- Conduct repeat mpMRI scan at 12 months after baseline
- Consider deferring routine 12-month biopsy if patient is considered low risk of progression or re-classification, (e.g. stable mpMRI and PSA)
- Perform DRE at 12 months where mpMRI is contraindicated
- Offer a repeat biopsy when mpMRI shows a suspicion of progression or if there is evidence of PSA changes (e.g. the individualised PSA threshold is breached)

Year 2

- Update personalised plan
- Repeat PSA test in line with PSA test interval and threshold (as above)
- Consider repeat mpMRI if a lesion was visible at baseline or the PSA rises and breaches the individualised PSA threshold
- Consider DRE on an individual basis
- Periodically review clinical assessment of suitability for radical treatment

Access to clinical nurse specialist

Men offered psychological support

Resume active surveillance as appropriate

continues on next page
Active surveillance continued...

Has the patient's preferences, co-morbidities or life expectancy changed? or Is there a sign of progression: has the PSA risen and/or an indication of radiographic progression that a biopsy has confirmed as clinically significant cancer?

Yes

Offer alternative management / treatment strategies

• Surgery
• External Beam Radiotherapy
• Brachytherapy
• Hormone therapy
• Watchful waiting

See Treatment Pathway Commentary for more information on recommendations to move to active treatment.

No
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

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

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

Active surveillance as optimal treatment unless patient chooses surgery.

Suitable for surgery?

Yes

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.

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.

No

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

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.

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Surgery – radical prostatectomy continued...

- Pre-operative 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

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

Stratified follow-up
- Six-week post-op PSA test
- Follow-up six to eight weeks
- PSA re-testing at three months and six months
- Annual follow-up

PSA remains low or at 0?
- No

PSA remains persistent?
- Yes

PSA rises three times?
- Yes

After at least two 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?

No

Yes

What is the patient's stage of disease?

Localised low and intermediate risk T1b–3a, Gleason < 8, any PSA

Locally Advanced (N0, any T3/T4, N1MO)

Metastatic prostate cancer (M1)

Does the patient have ≥ four metastases, including one outside the pelvis and spine or visceral metastases?

Yes

Go to Chemotherapy Pathway

No

Offer medical castration (luteinising-hormone-releasing hormone [LHRH] agonist) as androgen deprivation therapy, six months prior and for one-three years after. Include co-administration of an antiandrogen to LHRHα to prevent testosterone flare – one week before and three weeks after the first injection. Administer for four weeks.

In case of recurrence, men exposed to 78gy will not have the option of additional radiotherapy.

78gy in 37 fractions over seven to eight weeks

Intermediate risk T2a: hypo-fractionated high-dose IMRT

T2b and T2c–3a: IMRT

Optimal treatment administration.


Low risk (T1a): go to Active Surveillance pathway

Localised low and intermediate risk T1b–3a, Gleason < 8, any PSA

Consider short-term ADT for < six months

Consider short-term ADT for > six months

60 gy in 20 fractions over four weeks

Is the patient T3/T4, Gleason ≤ 7 and PSA < 40?

No

Is the patient at least two of: T3/T4 disease, Gleason 8–10, and PSA ≥ 40 ng/ml or TanyN1MO?

No

Yes

Combine ADT with Radical Radiotherapy (EBRT) – NICE Guidelines 2014

Is the patient able to tolerate chemotherapy?

Yes

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 (six to eight weeks) including: diarrhoea, rectal pain, unusual urinary frequency.

Consider short-term ADT for > six months

Unsuitable for radiotherapy, explore alternative treatments for stage of disease (e.g. radical prostatectomy)

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External beam radiotherapy (EBRT) continued...

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

- Yes
  - Check testosterone levels
  - Staging investigation is undertaken to identify whether cancer is still present locally within the prostate or has metastasised.
  - Low testosterone
    - Go to Second-line Hormone Therapy Pathway
  - Normal testosterone
    - Continue to monitor with PSA measurements after six and 12 months

- No
  - Continue to monitor with PSA measurements after six and 12 months

- EBRT to a dose of 74-78gy Radiotherapy should be given in combination with long-term ADT (18 months to three years) +/-brachytherapy boost +/- pelvic nodes.
  - Optimal treatment for locally advanced disease: combination external beam radiotherapy and brachytherapy.

- 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.

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- Improve quality of life

- Go to Chemotherapy Pathway

- Go to Radical Prostatectomy Pathway

- Go to Radical Prostatectomy Pathway
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
  - Planning session in theatre; volume study – with estimate based on MRI.
  - Consider three to six months of hormone therapy to shrink prostate to acceptable size before proceeding to pre-operative assessment.
  - Start low-dose rate brachytherapy
  - Consider androgen deprivation therapy for up to three years for men with high-risk localised prostate cancer and discuss the benefits and risks of this option with them.
  - See Support Pathway for more information on pelvic radiotherapy side effects (section 3.4)

- No
  - Unsuitable for brachytherapy, explore alternative treatments: active surveillance or external beam radiotherapy or surgery
  - High-dose rate / low-dose rate brachytherapy + external beam radiotherapy (boost or in combination)
  - Do not offer brachytherapy alone to men with high-risk localised prostate cancer.
  - Offer men with intermediate and high-risk localised prostate cancer six months of androgen deprivation therapy before, during or after radical external beam radiotherapy.
  - See Support Pathway for more information on pelvic radiotherapy side effects (section 3.4)

Is the prostate less than 60cc?

- Yes
  - Is the prostate now adequately sized?
    - Yes
      - Consider three to six months of hormone therapy to shrink prostate to acceptable size before proceeding to pre-operative assessment.
      - Same day
    - No
      - Planning session in theatre; volume study – with estimate based on MRI.
      - Consider three to six months of hormone therapy to shrink prostate to acceptable size before proceeding to pre-operative assessment.
      - Same day
  - No
    - Is the prostate now adequately sized?
      - Yes
        - Planning session in theatre; volume study – with estimate based on MRI.
        - Consider three to six months of hormone therapy to shrink prostate to acceptable size before proceeding to pre-operative assessment.
        - Same day
      - No
        - Planning session in theatre; volume study – with estimate based on MRI.
        - Consider three to six months of hormone therapy to shrink prostate to acceptable size before proceeding to pre-operative assessment.
        - Same day

Is the prostate now adequately sized?

- Yes
  - Planning session in theatre; volume study – with estimate based on MRI.
  - Consider three to six months of hormone therapy to shrink prostate to acceptable size before proceeding to pre-operative assessment.
  - Same day

- No
  - Consider three to six months of hormone therapy to shrink prostate to acceptable size before proceeding to pre-operative assessment.
  - Same day

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

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

- Yes
  - Consider three to six months of hormone therapy to shrink prostate to acceptable size before proceeding to pre-operative assessment.
  - Same day

- No
  - Planning session in theatre; volume study – with estimate based on MRI.
  - Consider three to six months of hormone therapy to shrink prostate to acceptable size before proceeding to pre-operative assessment.
  - Same day

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

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 three years.

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

Is there a sign of biochemical recurrence? (Two-three 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.

Continue to monitor with PSA measurements after six and 12 months

Localised / locally advanced

Metastatic

Is the patient symptomatic?

Yes

No

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

Monitor for symptoms

Go directly to M1 pathway

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)
Hormone therapy (first line): Locally advanced and metastatic prostate cancer

What is the patient's stage of disease?

Locally Advanced (N0 anyT3/T4, N1MO)

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

Consider (luteinising-hormone-releasing hormone [LHRH] agonist) for advanced hormone-dependent prostate cancer in patients with spinal metastases who present with signs or symptoms of spinal cord compression – no anti-androgen needed

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.

It may be possible to manage some of these side effects with diet and exercise.

Is the patient able to tolerate radical treatment?

Yes

- Is the patient T3/T4, Gleason ≤ 7 and PSA < 40?
  - Yes
  - Does the patient have ≥ four bone metastases, including one outside the pelvis and spine or visceral metastases?
    - Yes
    - Go to Radiotherapy Pathway
    - No
  - No
  - Is the patient at least two of: T3/T4 disease, Gleason 8-10, and PSA ≥ 40 ng/ml or TanyN1MO?
    - Yes
    - Is the patient able to tolerate chemotherapy?
      - Yes
      - No
      - continues on next page
    - No
  - No

No

- Is the patient able to tolerate radical prostatectomy?
  - Yes
  - Consider radical prostatectomy
  - No
In patients with measurable disease, progression is a rising PSA after three 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 two new metastases on a bone scan confirmed by appearance of at least two more on another scan performed at least six 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/T4 disease, Gleason score of 8-10, and prostate-specific antigen ≥ 40 ng/ml)
- Metastatic (TanyNanyM1a-c)

**Has the patient’s cancer progressed?**

- No
  - Go to External Beam Radiotherapy Pathway (if not had previously) and follow for locally advanced prostate cancer. For all stages continue castration therapy for up to three years total (in the absence of disease progression)
- Yes
  - Initial = rising PSA or the appearance of new metastases with castrate levels of testosterone
  - 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

**See External Beam Radiotherapy Pathway**

**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.

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

**For patients with locally advanced prostate cancer:**

- Go to External Beam Radiotherapy Pathway (if not had previously) and follow for locally advanced prostate cancer. For all stages continue castration therapy for up to three years total (in the absence of disease progression)

**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/T4 disease, Gleason score of 8-10, and prostate-specific antigen ≥ 40 ng/ml)**

**Metastatic (TanyNanyM1a-c)**

**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
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      - 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

**See External Beam Radiotherapy Pathway**
Chemotherapy

High-Risk Locally Advanced (At least two of: T3/T4 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

What is the patient’s stage of disease?

Metastatic prostate cancer (M1)

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

No

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

Does the patient have ≥ four bone metastases, including one outside the pelvis and spine or visceral metastases?

Yes

Is the patient able to tolerate chemotherapy?

No

Continue ADT 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

Go to Radiotherapy Pathway

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

Yes

Come from the Radiotherapy Pathway

Optimal treatment.

Monitor PSA – measurements after six and 12 months

See Support Pathway (section 3.8) for men with advanced metastatic prostate cancer.

continues on next page
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