

**PROFESSIONAL
SUPPORT**

Prostate Cancer UK's Best Practice Pathway

TREATMENT

Stage 2: Treatment pathway

Just as every man is an individual, every treatment pathway is individual and needs to be tailored to the needs of the man. Each man must have the opportunity to make an informed choice about their treatment pathway. They must be given detailed information about the treatments available for the stage of their disease, the side effects associated with each of these treatments and the outcomes the treatments will provide. For men with low risk cancer, active surveillance must be presented as a treatment option alongside surgery and radiotherapy.

Best practice

There are some key interventions, support services and medical research trial outcomes that demonstrate best practice for men. We believe these should be applied throughout the treatment journey and we provide examples of them throughout this treatment pathway.

Variation in treatment access

In 2016, all new prostate cancer treatments entered into baseline commissioning in England, Wales, Scotland and Northern Ireland. Despite this, treatment options for both localised and more advanced prostate cancer are varied in availability across the UK. Variation in availability, not being told about available treatments, or not being given full and balanced information about treatments can lead men to opt for a treatment that they may not have chosen, had they been given all available treatment choices. In order to minimise the potential for decision regret, it is therefore important that men fully understand what treatment options are available and the side effects each can cause; both physical and psychological. research shows that decision regret tends to occur between 6 - 12 months post-treatment¹.

Involving men and providing choice

We therefore recommend that healthcare professionals actively involve all men in making treatment choices and in care planning². To achieve this, the Urologist or Oncologist and the Cancer Nurse Specialist should provide men with both written and verbal [information](#)² and assist them in reaching an informed and balanced decision on their treatment pathway, checking that they have full knowledge of the outcomes. Where there is more than one appropriate treatment available then men should be able to speak to the relevant clinicians from the MDT concurrently. For example, if surgery and radiotherapy were both options the man should be able to discuss these options with both a Urologist and an Oncologist. When a treatment is not available at a specific hospital, men should be referred elsewhere to access their treatment choice.

Holistic Needs Assessment

A Holistic Needs Assessment (HNA) is a questionnaire that should be carried out at key points throughout the man's cancer journey. It is recommended that a HNA should be administered across the patient pathway (at diagnosis, pre-treatment, and then post-treatment).³

The HNA ensures that adequate care planning can take place and that, not only are physical concerns addressed but also individual needs relating to practical, relationship, emotional and spiritual concerns are considered too. It has been demonstrated that in carrying out a HNA is associated with improved quality of life and patient experience outcomes⁴. The overall process is supportive of patient-centred and collaborative care and is an effective means of targeting early intervention for the management of side effects and relevant support.

Delivering effective support

Full discussions about quality of life whilst undergoing and following treatment should be undertaken by the Consultant and CNS when counselling patients so the man and his loved ones fully understand the aims and consequences of treatment. The support pathway that accompanies this treatment pathway contains information on the specific prostate cancer related support needs of men for each treatment modality. It also

signposts to information that can support men's more generic cancer needs, for example, financial concerns.

Men choosing treatments that can be physically impairing (e.g. surgery, radiotherapy or hormone therapies) or have psychological impacts (active surveillance) should be given access to early interventions (e.g. penile rehabilitation, pelvic floor exercises and counselling/sources of support).

Men with prostate cancer may require supportive care at different stages of the patient pathway and from a range of service providers in both primary and secondary care. These include; in the community, hospitals, hospices, care homes and community hospitals. This means that healthcare providers need to work closely together to ensure that the needs of patients and carers are addressed, with no loss of continuity. Effective communication across service providers is essential, especially between primary and secondary care; in particular, for those men who opt for monitoring and surveillance or drug-based therapies where care may be delivered in either setting.

Evidence suggests that patients whose cancer is managed by an effective, integrated multi-disciplinary team (MDT) have better outcomes. There is also evidence that the multi-disciplinary management of patients increases their overall satisfaction with their care⁶. By being familiar with the complete spectrum of management strategies, the multi-disciplinary team can effectively support men throughout their treatment pathway, taking account of co-morbidities, age and social factors⁷; with ongoing support from the wider team to manage pain and the adverse effects of therapy.

2.1 Stages of disease

- Low risk localised prostate cancer
- Intermediate risk localised prostate cancer
- High risk localised prostate cancer
- Locally advanced prostate cancer
- Metastatic hormone sensitive prostate cancer
- Castrate resistant prostate cancer

2.2 Treatment options by stage of disease

See treatment by [risk stratification table](#).

2.3 Active surveillance

What is it and which men are suitable?

Active surveillance is a conservative management strategy for men with low or intermediate-risk, localised prostate cancer that allows them to delay or avoid radical treatment⁸. It is not a curative treatment.

On active surveillance, men's PSA (prostate specific antigen) levels should be regularly monitored. The frequency of monitoring should be based on a personalised active surveillance plan, developed by the urologist to include details of PSA interval and individualised PSA thresholds for follow up and re-assessment⁹. The patient should also have:

- a mpMRI at baseline
- a repeat scan 12 months after baseline and
- a prostate biopsy only when the PSA and MRI scan show signs of cancer progression.

Monitoring should be done alongside routine consultations with the patient. This will enable his risk of prostate cancer progression to be regularly re-assessed. Monitoring should also make sure that the

psychological needs of the patient are addressed and, if curative treatment is required, it should be made available as early as possible.

A clinical consensus developed by Prostate Cancer UK⁹ to guide clinicians on optimal active surveillance monitoring promotes active surveillance as the primary treatment for men with a Gleason score of $\leq 3+3$. It also guides clinicians to consider active surveillance for men with intermediate risk localised prostate cancer which is defined as: Gleason score $\leq 3+4$ AND mpMRI T stage $\leq T2$ AND (biopsy and MRI should be concordant) AND PSA density ≤ 0.2 ng/ml²⁹. Active Surveillance is not suitable for men with a Gleason score of $\geq 4+3$ (with pattern 4 disease in > 2 cores or >5 mm of cancer in a single core) OR mpMRI T-stage $\geq T3a$.

Benefit to patients

Active surveillance enables those men whose initial prostate cancer diagnosis indicates a tumour type that is unlikely or slow to progress to avoid or delay radical treatment and its side-effects, including urinary, bowel and sexual dysfunction.

To ensure that men are being monitored safely, the Prostate Cancer UK active surveillance consensus statement⁹ should be followed.

The evidence for use of active surveillance

In a recent study by Tosoian et al¹⁰, 1,300 patients with favourable risk prostate cancer placed on active surveillance between 1995 to 2014 were followed up. The majority of the study population were those with 'very low risk' prostate cancer (men with PSA levels that weren't very high and that only small amounts of low-grade cancer were detected in no more than two cores of a standard biopsy) with a smaller number of 'low risk' prostate cancer patients. According to the results of the study, two patients died from prostate cancer. The prostate cancer specific survival rate was 99.9% at both 10 years and 15 years.

More recently, the UK based ProtecT trial¹¹ demonstrated that active monitoring is a safe and effective treatment for men with low risk prostate cancer. This randomised control trial studied the survival rates, disease progression and patient reported outcome measures¹² of 1,643 men undergoing active surveillance, radical prostatectomy and radiotherapy. Further information on the trial and its findings can be found in the ProtecT summary.

The support men should receive

Urologists and Specialist Nurses who manage men with prostate cancer should use available evidence that demonstrates the outcomes of treatment available for localised prostate cancer. This can support men to make an informed choice about the treatment option they choose. In addition to this, men should be told of the side effects associated with radical treatments. This will enable these men to weigh up whether they prefer to opt for active surveillance without the physical side effects caused by radical treatment or to actively treat the cancer, with full knowledge of the potential side effects.

Men choosing active surveillance could also be offered psychological support, if experiencing anxiety because of their treatment choice. <https://bmjopen.bmj.com/content/bmjopen/5/5/e006674.full.pdf>

Achieving quality of life

It has been documented that men on active surveillance report good quality of life¹³ and show no significant difference in health related quality of life compared to men undergoing radical treatment¹³. However it is important to be aware of the stress patients face with the diagnosis of prostate cancer and to evaluate the patient's mental health at the time of diagnosis and monitor this throughout the patient's follow up.

Case study

- [Guys model - Understanding Active Surveillance](#)
- [Developing an active surveillance pathway - NHS Lothian](#)

Cancer progression during active surveillance

In the UK, cancer progression during active surveillance has two common parameters: PSA velocity or rate of rise (PSA-DT) and progression of Gleason grade from 3+3 to a higher grade. Some centres also use MRI progression of disease as a marker of disease progression. The decision to offer radical treatment should also include several other factors.

NICE, in its 2008 Prostate Cancer Guidelines, promotes that the decision to proceed from an active surveillance regimen to radical treatment should be made in the light of the individual man's personal preferences, comorbidities and life expectancy. Other clinical experts promote the use of several factors in combination, as the basis for triggering radical treatment. These include the patient's pathology and radiology, biopsy and grade progression, as well as clinical progression. In short, they suggest radical treatment is made available for palpable disease or a change in the radiological or clinical stage of the tumour. They also suggest that the clinician must take account of patient characteristics.

The EAU Prostate Cancer Guidelines¹⁵ promote basing the decision to suggest active treatment on a change in the biopsy results (Gleason score, number of positive cores, length in the core involvement), or T-stage progression. The three main criteria for initiation of treatment in patients showing disease progressions are; PSA-DT of less than two years, re-biopsy of primary tumour to Gleason grade 4 or more, or more than 50% of positive cores showing cancer involvement. A PSA change (especially a PSA-DT <3 years) is, according to EAU Prostate Cancer Guidelines¹⁵, a less powerful indication for changed management based on its weak link with grade progression¹⁶.

Active treatment may also be instigated upon a patient's request.

We have patient information about active surveillance [in print](#) and [online](#)

2.4 Watchful waiting

What is it and who is suitable?

Watchful waiting is a monitoring modality for men with localised prostate cancer who are either not suitable for, or do not ever wish to receive, curative treatment. It instead involves the deferred use of hormone therapy when symptoms of progressive disease develop. It is not a curative treatment.

As such, watchful waiting is suitable for older men and those with medical co-morbidities, who have a shorter life expectancy and are therefore unlikely to benefit from radical treatment. Watchful waiting can be a treatment option for older men diagnosed with a prostate cancer that is unlikely to interfere with quality of life or survival in the long term. It is also a suitable solution for men who do not wish to proceed with any other treatment modality to ensure that they remain to be monitored for disease progression and symptom related issues.

In comparison to active surveillance, watchful waiting involves fewer follow up visits and PSA levels to be checked, as shown in table 4.¹¹⁵

Table 3: Characteristics of active surveillance vs watchful waiting¹⁵

	Active surveillance	Watchful waiting
Follow-up	Predefined schedule	Patient-specific
Assessment/markers used	DRE, PSA, mpMRI, re-biopsy	Not pre-defined
Aim: life expectancy	Minimise over-treatment without compromising survival >10 years	Minimise treatment toxicity <10 years
Comments: aim	Only for low risk patients Minimise over-treatment without compromising survival	Only for localised disease until symptoms of progressive disease develop Minimise treatment toxicity
Comments	Only for low risk patients	Only for localised disease until symptoms of progressive disease develop

DRE = digital rectal examination, PSA = prostate specific antigen, mpMRI = multiparametric magnetic resonance imaging

Benefits to patients

Unlike active surveillance, watchful waiting relies on changes in a man's symptoms rather than disease progression to decide if treatment is needed. This means that patients are treated according to their symptoms and PSA levels in order to maintain quality of life¹⁵.

In addition, as there is no predefined assessment protocol for monitoring progression through markers, the need for annual biopsy is removed and follow up can usually take place in primary care. This reduces the need for men to attend hospital consultations.

Quality of life

Men may be affected psychologically and physically by knowing that they are living with an untreated tumour¹⁷ and may find it difficult to accept that their cancer is not being treated. It is therefore important that men are fully informed of all risks and benefits of watchful waiting, especially in relation to comorbidities and the effect that radical treatment may have on these. These men should also be reassured that there may be other treatment options available should the cancer progress to a stage where they become symptomatic or wish to commence a treatment protocol, though not curative.

Cancer progression during watchful waiting

Localised disease

As many small, localised, well-differentiated tumours do not progress, NICE recommends that a member of the urological MDT reviews men who have chosen a watchful waiting regimen and who have evidence of significant disease progression, especially a rapidly rising PSA level or bone pain⁸.

Locally advanced disease

In a randomised controlled trial investigating deferred treatment in men with locally advanced prostate cancer, 985 patients with T0-4 N0-2 M0 prostate cancer were treated with androgen-deprivation therapy (ADT) either immediately or after symptomatic progression or occurrence of serious complications. After a median follow-up of 12.8 years, there was no significant difference in prostate cancer mortality or time to castration-resistant progression between the two groups¹⁹. The study concluded that, outside of high-risk patients (those with a baseline PSA deferred) treatment is safe and reduces the need for, and time on, ADT.

We have patient information about watchful waiting [in print](#) and [online](#)

2.5 Surgery – radical prostatectomy

What is it and which men is it suitable for?

Radical prostatectomy (RP) involves removal of the entire prostate gland between the urethra and bladder, and resection of both seminal vesicles, along with sufficient surrounding tissue to obtain negative margins. Often, this procedure is accompanied by bilateral pelvic lymph node dissection.

For this reason it is usually offered to men with localised disease who have few or no co-morbidities⁸. Men with locally advanced disease can be considered for surgery when there is a realistic prospect of disease control, but they should be advised that there is a chance secondary treatment in the form of hormone therapy or radiotherapy may be required following surgery¹⁵.

The risk of having positive lymph nodes in intermediate-risk prostate cancer is between 3.7 - 20.1%²⁰. An extended lymph node dissection should be performed in intermediate and high-risk prostate cancer if the estimated risk for pN+ exceeds 5%²¹. This will improve staging. It should be considered in other cases whether extended lymph node dissection can be omitted, which means accepting a low risk of missing positive nodes. A recent meta-analysis showed there to be no benefit from lymph node dissection for low risk prostate cancer²².

The incidence of organ-confined disease is 26 - 31% in Gleason 8-10 lesions²². Patients with high-grade tumours confined to the prostate at histopathological examination have a good prognosis after radical prostatectomy²². These men may benefit most from potentially curative resection.

Radical prostatectomy may be offered via a robotically-assisted, laparoscopic, open retropubic or perineal approaches. A man's decision will be based on full counselling of the surgical options available. This means he should be informed about the overall advantages and disadvantages each available technique carries, specifically in relation to side effects, which include erectile dysfunction and urinary incontinence. It is also important that the surgeon performing the procedure discusses his / her individual performance outcomes which are now in the public domain in the UK²³ and can be accessed here:

http://www.baus.org.uk/patients/surgical_outcomes/radical_prostatectomy/default.aspx

Benefits of radical prostatectomy

There has been a rapid expansion in minimally-invasive approaches to radical prostatectomy over the last 10 - 15 years. When compared with open prostatectomy (retropubic and perineal), robotic-assisted and conventional laparoscopic prostatectomy is associated with less blood loss and faster convalescence from surgery²⁴.

With the advances in robotic radical prostatectomy (and the introduction of intraoperative frozen section in some centres²⁵) it has now become possible to ensure nerve sparing whilst also preventing a positive margin²⁶ during surgery.

Peri-operative risks

Radical prostatectomy requires a general anaesthetic, and is therefore associated with standard risks of infection, bleeding and thrombosis, scarring and hernia formation. Further uncommon peri-operative risks comprise of urine leak, ileus, bladder neck contracture and rectal injury. For those men undergoing pelvic lymph node dissection additional risks include lymph leak, lymphocele formation, lymphoedema (leg swelling) and nerve damage. Multiple modern retrospective series from high volume centres have shown that perioperative complications are reassuringly low, irrespective of surgical technique.

Patients with active cancer or undergoing cancer treatment are seen to be at higher risk of developing venous thromboembolism (VTE) complications. The evidence presented by NICE shows that men undergoing radical prostatectomy are at a further increased risk of VTE, as the total anaesthetic and surgical time is more than 60 minutes²⁸. NICE makes a strict recommendation that for this reason the VTE prophylaxis should be extended to a total of 28 days post-operatively with low molecular weight heparin (LMWH)²⁸.

A national audit undertaken in 2012 demonstrated that only 61% of centres were compliant with the full VTE recommendation²⁷. All men should be assessed for contraindications of VTE prophylaxis ahead of surgery. Men should not be offered pharmacological VTE prophylaxis if the risks of bleeding outweighs the risk of VTE²⁹.

Late effects

Assuming there are no significant perioperative complications, urinary incontinence and erectile dysfunction represent the two main problems faced by men after radical prostatectomy.

Urinary incontinence is present immediately on catheter removal and is at its worst in the first two months after radical prostatectomy, followed by gradual improvement over time. Pelvic floor exercises are thought to be important in speeding up continence recovery after radical prostatectomy³⁰, although there is limited evidence to support improved incontinence outcomes in men who begin pelvic floor muscle strengthening prior to prostatectomy. Nevertheless, teaching men the correct technique of pelvic floor exercises prior to surgery can help them to understand the aims of the exercise and assist in functional use of the pelvic floor area.

Erectile dysfunction can affect as many as 80% of men following a prostatectomy³¹, with age, pre-operative erectile function and constitutional risk factors, such as diabetes, smoking and heart disease as the key predictors for this side-effect. It is usually within the first few months following surgery that the loss of spontaneous erections and subsequent damage to cavernous tissue through lack of oxygenation to the tissue occur³².

Where possible, nerve-sparing prostatectomy should be used to maximise the chance of preserving erectile function.

It is important to discuss the full impact of surgery with men and assess their pre-surgical baseline function along with co-morbidities, medications and lifestyle to determine how this may affect current sexual function and likely post-operative penile rehabilitation in order to successfully manage the patient's (and partner's) expectations and recovery goals³².

Cancer recurrence after radical prostatectomy

NICE recommends that all men diagnosed with localised prostate cancer should be assigned a risk category so that clinicians have this as one of the factors to predict recurrence⁸.

The presence of any detectable PSA is often interpreted as indicating a clinically significant relapse, but this could be the result of the presence of benign tissue in a small proportion of men. As such, the existence of residual disease that could lead to clinical progression is best identified by serial PSA measurement.

For men, whose PSA levels drop to 0 post-surgery, but then rises, radical salvage treatment should be made available.

Where PSA levels remain at the post surgery level and do not go down men should be recommended adjuvant treatment, as this is an indicator that there is some cancer left or present in the lymph nodes or that the cancer has metastasised. Predictors of recurrence after prostatectomy for nodal metastasised prostate cancer³³ include biochemical recurrence as an initial serum PSA 0.2 ng/ml, with a second confirmatory level of PSA > 0.2 ng/ml³⁴. The EAU Guidelines¹⁵ also refer to the number of involved nodes, the tumour volume within the lymph node, and capsular perforation of the nodal metastases. A lymph node density (defined as the percentage of positive lymph nodes in relation to the total number of analysed/removed lymph nodes) over 20% was found to be associated with a higher risk of recurrence than a density below 20%³⁶. A biopsy is not recommended.

Radical salvage treatment

Radical radiotherapy to the prostatic bed should be offered to men with biochemical relapse following radical prostatectomy when they have no known metastases.

There is emerging evidence that early salvage radiotherapy improves distant metastasis free survival³⁷.

Adjuvant treatments

Local control with radiotherapy may be beneficial in prostate cancer patients with metastasis in regional lymph nodes after radical prostatectomy when also treated with continuous adjuvant androgen deprivation therapy. The beneficial impact of adjuvant radiotherapy on survival in these patients is highly influenced by tumour characteristics. Men with low-volume nodal disease (<3 lymph nodes) and GS 7-10 and pT3-4 or R1 as well as men with three to four positive nodes are more likely to benefit from radiotherapy after surgery³⁵.

On this basis, NICE recommends offering men with intermediate and high-risk localized prostate cancer a combination of radical radiotherapy and androgen deprivation therapy, rather than either of these alone⁸.

A randomised controlled trial (RADICALS38) is comparing whether radiotherapy to reduce the chances of subsequent cancer recurrence and metastasis-free survival is more or less clinically effective than close observation with early salvage radiotherapy at the first sign of PSA recurrence.

Case Study

[Physio led pre-prostatectomy clinic](#)

Surgery vs radiotherapy

There is no strong evidence for the benefit of surgery over radiotherapy or vice-versa. However, radical prostatectomy is a major operation that is typically only offered to fitter men without co-morbidities.

We have patient information about radical prostatectomy [in print](#) and [online](#)

2.6 Radical radiotherapy

What is it and which men is it suitable for?

Radiotherapy is the use of ionising radiation to treat cancer. The aim of treatment is to deliver a high enough dose of radiation to the tumour whilst at the same time keeping the dose to normal tissue as low as possible, to minimise complications. Both normal cells and malignant cells are damaged by the radiation, but if doses to normal tissue are kept low enough, the normal tissue should repair over time.

Radiation can be delivered externally, via external beam radiotherapy or internally via brachytherapy. When administered as mono-therapy, both external beam radiotherapy and brachytherapy are treatment options for men with low risk localised prostate cancer. Alternative options may include radical prostatectomy (surgery) or active surveillance.^{8,15}

For men with intermediate risk disease, external beam radiotherapy can be used in combination with hormone therapy to improve its effectiveness and is often standard practice. The hormone therapy will usually be given for three to six months. High dose rate brachytherapy can also be used in combination with external beam radiotherapy for this stage of disease and is postulated to be more effective⁸. In 2014, NICE recommended considering its use⁸.

For men with high risk localised or locally advanced prostate cancer, radical radiotherapy combined with two to three years of hormone therapy is the preferred treatment of choice^{8,15}. NICE recommends brachytherapy should not be considered as a monotherapy for men with high risk localised disease³⁹. It can however, be used for this stage of disease in combination with external beam radiotherapy. NICE document that actuarial five-year survival with high dose rate brachytherapy (see section below) in combination with external beam radiotherapy was found to be greater than with external beam radiotherapy alone (86% versus 54%, respectively; $p < 0.001$)⁴⁰. Five-year biochemical control (assessed by measurement of prostate-specific antigen [PSA]) has been shown to be more common with high dose rate brachytherapy in combination with external beam radiotherapy than with external beam radiotherapy alone (67% versus 44%; $p < 0.001$)⁴⁰. Men who undergo both external beam radiotherapy and brachytherapy, however, may find that they experience slightly worse side effects owing to the additional dose of radiation⁴¹.

Men with pelvic lymph node spread, but with no visceral or bony metastases, may also receive external beam radiotherapy to the pelvis to help control the local disease and they will also be receiving long term hormone therapy as standard⁴².

In addition to attempts at cure/control of cancer in the prostate gland, external beam radiotherapy can also be used in the form of palliative radiotherapy for symptom control in men with metastatic disease who are experiencing bone pain or complications from metastatic spinal cord compression⁸. It is also used very occasionally in the management of haematuria and bowel obstruction⁸.

External beam radiotherapy

External beam radiotherapy typically uses high energy x-rays, produced by a specially designed treatment machine. The most common type of treatment machine is called a Linear Accelerator. Other, less common machine types include a Tomotherapy unit (which looks more like a CT scanner) and a Cyberknife unit. The radiation is produced by the machine and directed into the body of the patient, to the intended target.

To limit side-effects to surrounding tissues, external beam radiotherapy was conventionally delivered by crossing beams of x-rays which are angled towards the prostate, a technique known as 3D conformal radiotherapy. The treatment beams could be planned/tailored to precisely match the shape and size of the prostate (or wider pelvic volume) in all three dimensions, which meant that the largest dose of radiotherapy was received by the prostate, with much smaller doses to surrounding tissues.

More recently intensity modulated radiotherapy (IMRT), an advanced form of 3D conformal radiotherapy, has emerged. Intensity modulated radiotherapy uses sophisticated computer programs to direct different doses of radiotherapy to different areas of the prostate and pelvic organs, and is now the preferred method of delivering radical radiotherapy to the prostate in many radiotherapy departments. It has been shown to reduce the dose planned to the rectum⁴³, and even with increases in the dose prescribed, produces acceptable toxicity rates. It can also be used to deliver a therapeutic dose to the pelvic lymph nodes, whilst more effectively limiting the dose to the surrounding bowel.

It is important that the patient, and the position of their internal anatomy, remains as stable as possible. It is universal for radiotherapy departments to use devices to help stabilise a man's legs and/or pelvis. It is also common for them to ask a man to maintain a particular bladder and rectal status. Daily changes in the rectal or bladder status, depending on how full or empty they are, can alter the position of the prostate.

A commonly prescribed course of radiotherapy is 78 Gray (Gy) given in 37 fractions over seven to eight weeks. However, recent trials have shown that splitting the same total dose into fewer fractions – hypofractionation – can shorten the course of radiotherapy without increasing side effects⁴⁴.

The CHHiP (Conventional or Hypo-fractionated High dose Intensity Modulated Radiotherapy for Prostate Cancer) trial⁴⁴ used intensity modulated radiotherapy to deliver a hypo-fractionated dose prescription, in order to compare its effectiveness with the standard recommended dose. It showed that 60gy given in 20 fractions over four weeks controlled the cancer as effectively as a higher dose over a longer time and did not cause increased side-effects. Men attended 17 fewer appointments. This should be standard care.

Arm H of the Stampede trial⁸⁷ found that radiotherapy to the prostate improved overall survival in men with a low metastatic burden. Three-year overall survival for men who were given radiotherapy targeted to their prostate (intervention) was 81% compared to men who just receiving ADT and/or docetaxel (standard) which was 73%. This increase in overall survival is significantly significant. The definition used for low metastatic burden is patients who do not have ≥ 4 metastases, including 1 outside the pelvis & spine or visceral metastases. Currently there are no clinically significant results to determine whether the patients with low metastatic burden should have radiotherapy targeted to the prostate before or after chemotherapy.

Benefits of external beam radiotherapy

For most men with localised disease who need treatment, radical external beam radiotherapy has comparable rates of disease control and overall survival when compared with radical prostatectomy¹¹. External beam radiotherapy does not require a general anaesthetic however, meaning that men can avoid the risks of anaesthesia and occasional immediate operative complications such as bleeding, infection and thrombosis.

Although there are recognised side-effects during radiotherapy, which are discussed below, many men will undergo treatment with very few problems, and a resultant good quality of life after treatment. The daily hospital attendance required for treatment can also be a welcome source of peer support from other men with prostate cancer, as well as allowing regular access to the radiotherapy team.

Risks of external beam radiotherapy

Short-term side-effects

During treatment, there are several initial, short-term side effects that a man may experience. These develop a few weeks into treatment and peak at the end of treatment and in the few weeks after treatment has finished. They usually last for six to eight weeks. The most common symptoms arise from irritation and inflammation of the bladder and bowel. When side effects are at their peak, men may find it more difficult to hold urine within their bladder and may experience an overwhelming urge to urinate. The fear of incontinence/leakage can be distressing and incontinence pads may be something a man wants to consider. Pelvic floor exercises can help to control the flow of urine.

Fatigue can also be a result of external beam radiotherapy and can be exacerbated by any anxiety or distress caused by the cancer or its treatment, and/or other issues such as the daily journey for treatment, or lack of sleep due to an increased need to urinate at night. To manage and cope with the fatigue, it is important that men remain physically active and maintain a healthy diet. Resistance exercises can help maintain muscle strength, which can reduce whilst on hormone therapy.⁸

Nowadays, the techniques used in external beam radiotherapy can be very effective at minimising the dose to the bladder, rectum and bowel. As a result, the side effects are relatively mild and manageable for many men.

For those men receiving radiotherapy in combination with androgen deprivation therapy they will also experience the side effects that are common with hormone treatment and are related to a reduction in circulating testosterone. This can include fatigue, low mood, loss of libido and erectile dysfunction.

Late effects

Long-term effects can occur months to many years after radiotherapy and the risks vary depending on the areas included in the field of radiation and the radiation techniques that were used, as these continue to develop and improve. Some of the potential long-term side effects of radiation to the prostate include:

- urinary problems that are potentially the result of urethra stricture (often more likely after combined external beam radiotherapy and brachytherapy. Symptoms include:
 - urinary retention
 - weak urinary flow
- bowel problems, which can require a sigmoidoscopy to check for any bowel damage
- erectile dysfunction
- hip and bone pain and/or weakness.

As with other side effects men should be encouraged to adopt a healthy diet and engage in regular exercise. Smoking cessation should be promoted⁴⁵. Early intervention with the use of PDE5 inhibitors and/or vacuum erection devices (VED) is recommended as a means of preserving erections and promoting rehabilitation. A conservative approach through exercise planning, lifestyle changes and pelvic floor exercises may also be helpful⁴⁵.

Finally, external beam radiotherapy is associated with an increased risk of the development of bladder and rectal cancer many years later. These cancers are quite rare in the general population and therefore the additional risk for men receiving external beam radiotherapy remains small.

More information on the late effects of radiotherapy and their management is contained in the support pathway.

We have patient information about external beam radiotherapy [in print](#) and [online](#).

Brachytherapy

Brachytherapy is a method of accurately delivering a measured dose of radiation to a target organ. Like all radiation techniques, the aim is to maximize the dose to the target organ whilst sparing sensitive normal tissue⁴⁶. When radiation is used to treat most solid tumours, the dose required to achieve clinical benefit exceeds the tolerance of normal tissues and will potentially cause damage to the surrounding tissues and organs. It allows for doses of over 100 Gy to be delivered.

Prostate brachytherapy can be delivered through two different mechanisms; low dose rate (commonly known as permanent seed brachytherapy) or high dose rate.

Mechanisms of brachytherapy

Low dose rate brachytherapy (LDR / permanent seed brachytherapy)

Low dose rate (LDR) brachytherapy involves the implantation of radioactive seeds through fine needles into the prostate under ultrasound guidance. The seeds emit radiation over several weeks or months and remain in situ permanently. LDR will usually be administered in a day case setting under general or spinal anaesthetic. It is often however not used in men whose prostate is >60 - 80cc, those men with significant urinary symptoms (IPSS >12), a poor urinary stream, or a history of prostate outflow surgery. NICE Guidelines recommend its use as a standard of care for low-risk localised prostate cancer and it is increasingly considered as effective as radical prostatectomy^{47,48} when direct comparison in identical risk stratified populations has been undertaken. However, its role in high risk disease is less clear.

External beam radiotherapy (in combination with hormone therapy) is often used to treat men with high-risk localised prostate cancer. This can be combined with a brachytherapy boost (see high-dose rate brachytherapy below). The ASCENDE-RT trial, which published in 2017, randomized 398 men to either a standard arm with 12 months of androgen deprivation therapy, pelvic irradiation to 46 Gy, followed by a dose-escalated external beam radiation therapy (DE-EBRT) boost to 78 Gy or an experimental arm that substituted a low-dose-rate prostate brachytherapy (LDR-PB) boost. It showed that a low-dose-rate boost improved biochemical-progression free survival by 20% at 9 years' follow-up in contrast to dose-escalated external beam boost⁴¹.

It is important to bear in mind that the ASCENDE-RT trial had a small sample size. The trial did not show any improvement in overall prostate cancer survival between the two arms. There was also a long interval from local recurrence to life-threatening disease, which can mean that competing causes of mortality can erode any potential survival benefit associated with improved local control. Furthermore, whilst more than 80% of patients reported no side effects at 5 years' follow up, incidence and prevalence of moderate to severe genitourinary morbidity, frequency and severity of urinary incontinence and the need for late stage catheterisation were all higher in men treated with low dose rate boost compared with high dose⁴⁹. For these reasons, low-dose rate brachytherapy as a boost to androgen suppression and dose escalated radiation therapy should only be considered as a treatment option for men with high and intermediate risk prostate cancer. The choice between low-dose rate or high-dose rate brachytherapy is best based on clinical judgement and patient choice.

High dose rate brachytherapy (HDR / temporary brachytherapy)

High dose rate prostate brachytherapy is predominantly used as a boost to external beam radiotherapy in men with intermediate (when Gleason score is 4+3), high-risk localised, and locally advanced prostate cancer. NICE recommends that men with these stages of the disease are offered six months of ADT before, during or after radical external beam radiotherapy. NICE also recommends that ADT is considered for up to three years for men with high-risk localised prostate cancer and that the benefits and risks of this option are discussed with them. ADT should be used alongside EBRT and HDR brachytherapy for men with locally advanced disease.

Very occasionally it may be used as a sole treatment for intermediate risk localised disease, but it should not be used as a sole treatment for men with high risk localised prostate cancer.

In HDR brachytherapy thin plastic catheters are inserted through a template, through the perineal skin, and into the prostate gland. A radioactive source is then inserted into each tube. A computer controls how long the radioactive source remains in each of the tubes, so that the amount of radiation can be targeted effectively. This allows a higher dose to be given to the tumour tissue than to the urethra and rectum. The catheters are then removed, leaving no radioactive material in the prostate gland⁴⁰.

Benefit to patients

As with any treatment, there are recognised side effects, however, it has been shown that brachytherapy has reduced long-term risk of urinary incontinence and erectile dysfunction compared with other treatment options such as radical prostatectomy and external beam radiotherapy⁴⁶.

Brachytherapy is associated with a quicker recovery time because LDR can be administered as a day case (HDR will often involve an overnight stay). LDR is also a one-off treatment so there is no need for frequent hospital attendances as with some of the other treatment options available.

Support for men and ensuring quality of life

The surgical procedure to administer the radiation (such as haematuria and swelling) can make the side effects of brachytherapy both immediate and long-term. This can occur alongside the on-going effect of the radiation in the prostate.

Commonly reported side effects include;

- urinary problems including difficulty passing urine, radiation cystitis, urinary incontinence
- haematuria or haematospermia
- erectile dysfunction
- bowel problems including diarrhoea, frequent bowel movements, bleeding or proctitis
- fatigue
- seed migration (in men undergoing LDR only).

Not all men will suffer all or any of these side effects and other rarer side effects can occur, however, written information should be provided to all men that clearly explains the procedure and the side effects that they

may experience². Information should be given alongside those of comparative treatments along with the associated side effects of each treatment to ensure an informed choice can be made.

Men should also be given guidance on radiation safety, in particular regarding avoiding close contact with pregnant women, young children and pets⁴⁹. It is recommended that during the first two months following brachytherapy, children should not sit in close proximity to the patient or on the patient's lap for more than a few minutes a day⁵⁰. Men should also avoid sitting in close proximity to pregnant women for long periods of time⁵⁰.

For men who have received permanent seed implantation, the use of a condom for the first five ejaculations is recommended due to the small risk that a seed may be contained within the ejaculate. Condoms should be double wrapped and placed in the dustbin for disposal⁵⁰. Expelled brachytherapy seeds should not be picked up by hand. Should a seed be expelled either through ejaculation or urination it should be picked up with tweezers or a spoon and flushed down the toilet⁵⁰. It is important that the patient knows to inform their oncologist should any of the seeds be expelled as this can impact on the overall dosimetry and in the majority of cases, if seeds are expelled through urination it is likely to happen shortly after implantation⁵⁰.

Men and their caregivers should also be made aware that if the patient passes away within 20 months of their seed implantation, the relevant persons should be informed ahead of a post-mortem or cremation so that radiation risks can be assessed appropriately⁵⁰.

We have patient information about brachytherapy about permanent seed brachytherapy ([print](#) and [online](#)) and HDR brachytherapy ([print](#) and [online](#))

Cancer progression and recurrence after radical radiotherapy

The PSA does not usually fall to zero after radical treatment with external beam radiotherapy or brachytherapy. The definitions of biochemical relapse with the best combination of sensitivity and specificity for clinical or distant relapse after radical treatment are those that used a fixed value above a nadir. This allows for the slight rise in PSA that is seen when neoadjuvant or adjuvant hormone therapy is discontinued. The 2005 ASTRO consensus definition (PSA greater than current nadir + 2 ng/ml) had a sensitivity of 74% and specificity of 71% for any clinical failure^{55, 56}.

In patients treated with brachytherapy, PSA levels may temporarily rise (the PSA bounce) after initial treatment and may not be an indicator of recurrence.

In patients with biochemical recurrence, a staging investigation is undertaken to identify whether cancer is still present locally within the prostate or has metastasised. Biopsies are only undertaken where the cancer remains localised. Multi-parametric MRI should be used for biopsy targeting and guiding local salvage treatment¹⁵. In patients who have biochemical recurrence but are still at a localised or locally advanced stage of disease, the path taken depends on if the patient is symptomatic. If asymptomatic, then the patient should be monitored for symptoms. For symptomatic patients, without metastases, curative salvage local therapies for biochemical relapse after radiotherapy include radical prostatectomy, cryotherapy and high intensity focused ultrasound. These men should not be offered routine MRI scanning prior to salvage radiotherapy. Patients with metastases should be offered hormone therapy in combination with docetaxel chemotherapy or if they have already received hormone therapy, they should be offered abiraterone or enzalutamide.

Support for men and ensuring quality of life

Curative salvage treatment for external beam radiotherapy recurrence can be difficult: men exposed to 78 grey will not have the option of additional radiotherapy. Those who have had lower doses may be offered brachytherapy (where available), but this would be done as part of a trial.

Curative salvage local therapies for biochemical relapse after radiotherapy include radical prostatectomy, cryotherapy and high intensity focused ultrasound. Radical prostatectomy as salvage has been shown to produce biochemical control in highly selected men but carries a higher risk of incontinence, impotence and

rectal damage than when used as primary treatment⁵². Evidence for the relative benefit of these options is limited: salvage surgery is the preferred treatment option of curative intent but, due to significant side effects, very few salvage radical prostatectomy operations are performed in the UK each year. If a man requires salvage surgery following brachytherapy, the potential for radiation risk must be considered.

If patients have a low-risk prognosis and are asymptomatic they should continue to be monitored with PSA measurements after 6 and 12 months. If there is a slow biochemical increase, they can be managed expectantly. If, however PSA levels begin to double in less than three months the introduction of hormone therapy should be considered for those men who have not yet had it and be given it in combination with docetaxel chemotherapy if they have metastasised. If a patient is already having hormone therapy, abiraterone or enzalutamide may be introduced.

In general, patient should not routinely offer hormone therapy unless the patient has:

- symptomatic local disease progression, or
- any proven metastases (where combination docetaxel should be made available) or
- a PSA doubling time of less than three months⁸.

Case Study

[Bath model – improving patient experience of radical radiotherapy](#)

External beam radiotherapy vs brachytherapy

There are no randomised trials comparing brachytherapy with other radical therapies or with watchful waiting. Systematic reviews of observational studies found insufficient evidence to compare overall and disease specific survival after brachytherapy with that after other radical therapies^{53–56}. Evidence from these systematic reviews suggests that, at least for low-risk patients, biochemical recurrence free survival after brachytherapy is equivalent to that after external beam radiotherapy or radical prostatectomy.

Evidence from systematic reviews comparing the toxicity of radical therapies for prostate cancer^{53,54,56} suggest brachytherapy has a similar adverse event rate to radical prostatectomy or external beam radiotherapy, but such comparisons are based on evidence from observational studies. Some reports of brachytherapy case series suggest lower rates of impotence and incontinence than seen with surgery or external beam radiotherapy but higher rates of obstructive and irritative urinary symptoms.

2.7 Hormone therapy – first line

What it is and who's suitable?

Hormone therapy, also known as Androgen Deprivation Therapy (ADT) is used to treat locally advanced and metastatic prostate cancer, with the aim of controlling disease progression. Prostate cancer cells usually require androgen hormones, such as testosterone, to grow. ADT can be achieved by either suppressing the secretion of testicular androgens or inhibiting the action of circulating androgens at the level of their receptor.

There is no level 1 evidence for or against a specific type of ADT, whether, luteinizing hormone-releasing hormone (LHRH) analogue or antagonist, except in patients with impending spinal cord compression for whom either a bilateral orchiectomy, or an LHRH antagonist are the preferred options¹⁵. There is, however, evidence to promote the use of androgen monotherapy (bicalutamide 150 mg) in men with locally advanced disease but not for metastatic disease⁸.

The initial testosterone flare associated with LHRH agonists can be prevented by co-administration of an antiandrogen⁵⁷. Prevention of 'flare-up' – also known as an androgen blockade – is important in symptomatic patients or when a clinical flare might lead to severe complications. Anti-androgen therapy is usually continued for four weeks but neither the timing nor the duration of anti-androgen therapy is based on strong evidence. NICE however recommends that men with metastatic prostate cancer are not offered combined androgen blockade as a first-line treatment⁸.

In symptomatic patients, immediate treatment is mandatory. However, controversy still exists for asymptomatic metastatic patients due to the lack of quality studies.

The PSA threshold at which ADT must be stopped or resumed still needs to be defined in prospective studies.^{58 59}

Luteinising-hormone-releasing hormone agonists

Long-acting LHRH agonists are currently the main forms of ADT. They are delivered as depot injections on a one-, two-, three-, six-monthly, or yearly basis. After the first injection, they induce a transient rise in luteinising hormone (LH) and follicle-stimulating hormone (FSH) leading to the 'testosterone surge' or 'flare-up' phenomenon, which starts two to three days after administration and lasts for about one week. LHRH products have differences in relation to whether they are ready for immediate use or not and the type of injection used to administer them¹⁵. LHRHa may be given alone (after a short period of anti-androgen therapy to prevent tumour flare) or in combination with an anti-androgen (see section on progression) as combined androgen blockade for men with metastatic disease⁸.

Gonadotrophin releasing hormone antagonists (GnRH)

GnRH antagonists are used less often than LHRH agonists⁵² and are sometimes referred to as GnRH blockers. There is currently only one type of GnRH antagonist available in the UK, called degarelix (Firmagon[®]), which can be used as a first line treatment for metastatic prostate cancer⁶⁰. It can help to prevent metastatic spinal cord compression (MSCC) for those men who have spinal metastases⁶¹ (see section 3.1), which can occur if cancer cells grow in or near the spine and press on the spinal cord.

Unlike LHRH agonists, degarelix immediately binds to LHRH receptors, leading to a rapid decrease in LH, FSH and testosterone levels without any flare⁶² and anti-androgen tablets are not required. Instead testosterone levels start to drop straight away and symptoms, such as bone pain, should start to improve quickly^{63,64}.

Anti-androgens

These are oral compounds that are classified according to their chemical structure as:

- steroidal, e.g. cyproterone acetate (CPA), megestrol acetate and medroxyprogesterone acetate;
- non-steroidal or pure, e.g. nilutamide, flutamide and bicalutamide.

Both compete with androgen receptors, but as this is the only function of non-steroidal antiandrogens, they lead to an unchanged or slightly elevated testosterone level. By contrast, steroidal antiandrogens have progestational properties.

In 2014, the NICE Guidelines recommended that men with locally advanced prostate are offered a combination of radical radiotherapy and androgen deprivation therapy, rather than radical radiotherapy or androgen deprivation therapy alone. The guidelines state that combining hormone therapy and radiotherapy treatments may provide optimal local and distant tumour control. However, this combined treatment is only relevant to those patients where radiotherapy alone would not encompass and eliminate the full extent of the prostate cancer. The hormones may be given for a variable length of time and may precede, be given during and for a period following radiotherapy. The optimal timing and overall duration is uncertain⁵².

Evidence also supports the use of docetaxel in combination with hormone therapy – and with or without external beam radiotherapy – as a treatment option for men with hormone-naïve, high-risk locally advanced prostate cancer.

Results from the meta-analysis accompanying the STAMPEDE trial data shows that offering docetaxel to men at this stage of the disease who are receiving long-term hormone treatment with or without radiotherapy, significantly reduced treatment failures, from 30% to 22% at four years⁷⁵. In addition, the control arm of the STAMPEDE trial showed progression to occur in about 72% of men after 5 years compared with about 62% with the addition of docetaxel⁶⁶. This includes men with metastatic and non-

metastatic prostate cancer. A similar benefit for docetaxel was seen in both groups; the hazard ratio for failure-free survival was 0.60 (95% CI 0.45-0.80) in men with non-metastatic disease, and 0.61 (95% CI 0.53-0.71) for men with metastatic disease. Men having standard treatment without the addition of docetaxel progress more quickly to hormone-refractory disease (median 15 months' difference)⁶⁶.

High-risk locally advanced disease is defined by the STAMPEDE trial as locally-advanced prostate cancer with at least two of: T3/4 disease, Gleason score of 8–10, and prostate-specific antigen ≥ 40 ng/ml⁶⁶. Patients should be of sufficient performance status to be treated with 6 cycles of docetaxel chemotherapy, with no clinically significant cardiovascular history.

The table below is replicated from the March 2016 update of the European Association of Urology Guidelines for prostate cancer¹⁵. It details hormonal treatment approaches for metastatic prostate cancer.

Recommendation	
In M1 symptomatic patients, offer immediate castration to palliate symptoms and reduce the risk for potentially catastrophic sequelae of advanced disease (spinal cord compression, pathological fractures, ureteral obstruction, extra-skeletal metastasis).	
In M1 asymptomatic patients, offer immediate castration to defer progression to a symptomatic stage and prevent serious disease progression-related complications.	
In newly asymptomatic M1 patients, offer castration combined with docetaxel, provided patients are fit enough to receive chemotherapy.	
In M1 asymptomatic patients, discuss deferred castration with a well-informed patient since it lowers the treatment side-effects, provided the patient is closely monitored.	
Anti-androgens	
In M1 patients treated with an LHRH agonist, offer short-term administration of anti-androgens to reduce the risk of the 'flare-up' phenomenon.	
Start anti-androgens used for 'flare-up' prevention on the same day as an LHRH analogue is started or for up to seven days before the first LHRH analogue injection if patient has symptoms. Treat for four weeks.	
Do not offer anti-androgen in monotherapy in M1 patients.	
Intermittent treatment	
Population	In asymptomatic M1 patients, offer intermittent treatment to highly motivated men, with a major PSA response after the induction period.
Threshold to start and stop ADT	In M1 patients follow the schedules used in published clinical trials on timing of intermittent treatment. Stop treatment when the PSA level is < 4 ng/mL after six to seven months of treatment. Resume treatment when the PSA level is $> 10 - 20$ ng/mL (or to the initial level if, 20 ng/mL).
Drugs	In M1 patients, offer combined treatment with LHRH agonists and NSAA.

Offer LHRH antagonists, especially in patients with an impending spinal cord compression or bladder outlet obstruction.

Benefits to patients

Hormone therapy offers a means for disease control. The function of hormone therapy on prostate cancer is to stop testosterone feeding prostate cancer and encouraging growth. ADT blocks the production of androgens including testosterone, with the aim of slowing the growth of prostate cancer cells.

Hormone therapy can be used alongside other treatments to make them more effective. The results of the UK STAMPEDE trial⁶⁵ demonstrated that the use of docetaxel at the time of initiation of androgen deprivation therapy significantly increased overall survival for men with metastatic or high risk, locally-advanced disease. Docetaxel is given once every three weeks by intravenous infusion over one hour for six cycles in this situation⁶⁶ (see section on Chemotherapy). It is also standard practice to combine hormone therapy with radical radiotherapy to treat intermediate and high risk localised and locally advanced tumours that have not yet spread to more distant locations, such as the bones (see section on Radical radiotherapy). Hormone therapy can also help to reduce some of the symptoms of advanced prostate cancer, such as urinary symptoms and bone pain and for men with high-risk features, such as high PSA and Gleason scores, there are some studies that suggest that the longer men receive hormone treatment, the better.

Two clinical trials that published in June 2017 have demonstrated the benefit of abiraterone in combination with Androgen Deprivation Therapy (ADT) for men with high-risk advanced prostate cancer. These trials include:

The phase III LATITUDE trial has shown that the addition of abiraterone acetate and prednisone to androgen-deprivation therapy resulted in marked improvements in overall and progression-free survival in patients with newly diagnosed castration-sensitive metastatic prostate cancer⁷¹.

The STAMPEDE clinical trial has shown that adding abiraterone acetate to a standard initial treatment regimen for high-risk, advanced prostate cancer (either locally advanced or metastatic cancer in men who were commencing long-term standard androgen-deprivation therapy for the first time) lowers the relative risk of death by 37%. The 3-year survival rate was 76% with standard therapy alone vs 83% with standard therapy plus abiraterone⁷².

It is important to note that both trials began after results from the STAMPEDE trial published in 2015 showed the combined use of docetaxel and ADT in men with newly diagnosed metastatic disease delivered an additional survival benefit of 15 months. Earlier docetaxel is now standard practice.

Without evidence to determine whether earlier abiraterone or earlier docetaxel (both in combination with ADT) will perform better in which men or it will perform better when combined, earlier abiraterone cannot be recommended as the new standard of care. The results from the PEACE1 trial may change this.

This pathway suggests the use of abiraterone acetate and prednisone with androgen-deprivation therapy in men with newly diagnosed metastatic prostate cancer who are contra-indicated for docetaxel. This of course can only be standard practice after NICE and the Scottish Medicines Consortium (SMC) approve its use on the NHS.

Risks to patients

Hormone therapy has an extensive side-effect profile, the main ones being:

- hot flushes,
- changes to your sex life,
- extreme tiredness (fatigue)
- weight gain
- strength and muscle loss
- breast swelling and tenderness
- loss of body hair
- bone thinning

- changes to your mood
- risk of heart disease, stroke and diabetes.

Cholesterol, especially low-density lipoprotein cholesterol also tends to rise, and muscle tends to get replaced by fat. Most men who are on hormone therapy experience at least some of these effects, but the degree to which any man will be affected by any one drug regimen is impossible to predict

Research continues to explore different ways to minimise the side effects of testosterone loss while maximizing the therapeutic effect of hormone therapy. The most commonly explored strategy is known as intermittent therapy, which is given to those men who cannot tolerate the side-effects.

This strategy takes advantage of the fact that it takes a while for testosterone to rise again after LHRH agonists are removed. With intermittent hormone therapy, the LHRH agonist is used for up to twelve months, during which time a low PSA level is maintained. The drug is stopped until the PSA rises to a predetermined level, at which point the drug is restarted. The 'drug holidays' in between cycles allow men to return to nearly normal levels of testosterone, potentially enabling sexual function and other important quality of life measures to return before the next cycle begins again.

At this time, however, the true benefits of this approach remain unclear⁶⁷, and large clinical trials are currently underway to evaluate its use in men with advanced prostate cancer. If the approach proves to be as effective as continuous therapy in suppressing tumour growth, intermittent therapy will likely become popular because of potential for an improved side effect profile.

NICE recommends that men having intermittent androgen deprivation therapy should:

- have their PSA measured every three months **and**
- restart androgen deprivation therapy if PSA is 10 ng/ml or above, or if there is symptomatic.

Support for men and ensuring quality of life

It is important that men receiving hormone therapy are regularly monitored, especially in relation to bone health, cardiovascular health, diabetes, anaemia and sexual function. Referrals to relevant specialists should be made as soon as symptoms occur.

For other side-effects, recommendations should be made to ensure a healthy diet, regular exercise and regular sleep patterns and routines are followed.

Detailed management approaches for side-effects including fatigue, erectile dysfunction and sexual desire loss are contained within the support pathway.

Case study

[Healthy on Hormones](#) – Guy's Hospital

Progression

Initial progression on ADT is usually defined as a rising PSA or the appearance of new metastases with castrate levels of testosterone. As this is a signal that monotherapy LHRH has failed, an anti-androgen may be added as second-line hormonal therapy.

Other treatments are also available but used less commonly. These include estrogens and steroids. Estrogens help to inhibit androgen production by the testicles, while steroids can help the adrenal glands to produce less testosterone. Steroids may also help improve appetite and energy levels and can treat pain.

Subsequent progression is harder to agree. The disease can be considered to be castrate-resistant when androgen deprivation therapy or combined androgen blockade are no longer controlling PSA levels or the symptoms of the disease, or when there is radiological evidence of progression. However, castrate-resistant disease may still respond to agents such as abiraterone. Rising PSA alone should not be considered

progression. However, in the context of clear increase in symptoms, this may be sufficient to define progression even without confirmed radiological progression.

In patients with measurable disease, progression would usually be the appearance of new soft tissue metastases or a clear increase in size of existing metastases (usually at least a 20% increase in size). If bone metastases, then this requires the appearance of at least two new metastases on a bone scan confirmed by the appearance of at least two more on another scan performed at least six weeks later.

Even when the disease becomes castrate-resistant, the androgen receptor on the cancer cells can remain active and LHRH therapy is usually continued. There is no known curative therapy for hormone-relapsed disease and so the goals of treatment are to improve survival and quality of life and to control symptoms.

We have patient information on hormone therapy in [print](#) and [online](#)

2.8 Hormone therapy – second line

What it is and who's suitable?

Although first-line hormone treatments for prostate cancer reduce testosterone levels, testosterone and other male hormones (androgens) continue to be produced in other tissues and can stimulate prostate cancer growth. Abiraterone and enzalutamide are potent inhibitors of male hormones (androgens) in testicular, adrenal and prostatic tissues. Weaker anti-androgens such as bicalutamide can sometimes be used after first-line hormone injections have stopped working and PSA levels are slowly going up. They are used in combination with an LHRHa, but the decision to do so will also be based on an individual's age, rate of PSA rise and frailty. Increasingly they have been replaced by abiraterone or enzalutamide, which are now considered optimal practice. These drugs can be added to first-line hormone injections when there are signs that the injections alone are no longer controlling the cancer – this is known as castrate-resistant prostate cancer – and would be an alternative treatment option for men who are contraindicated for chemotherapy or have failed to get access to docetaxel chemotherapy within 12 weeks of starting hormone therapy (see section 2.9)

Abiraterone or enzalutamide can also be used after chemotherapy with docetaxel. However, the NHS restricts their use to only one drug, either abiraterone or enzalutamide, before or after chemotherapy, because there is poor evidence for any benefit using them in sequence.

Abiraterone

What it is and who's suitable?

Abiraterone can be used to treat men whose prostate cancer has spread beyond the prostate and who have had previous treatment with hormone therapy injections (goserelin, leuprorelin, triptorelin or degarelix). It can be given either before or after chemotherapy with docetaxel if this is being considered. Some men cannot be treated with chemotherapy (see section 2.9). Abiraterone blocks the production of corticosteroids by the adrenal glands so it must be given with the steroid prednisolone. Both drugs are taken by mouth in tablet form.

Benefits to patients

Abiraterone prolongs survival of men with metastatic castrate-resistant prostate cancer by about four months whether it is given before or after chemotherapy^{68,69}.

Support for men to ensure quality of life

The most common side effects with abiraterone are tiredness, anaemia, diarrhoea, fluid retention and a rise in blood pressure. It is important to measure blood pressure regularly. It may also affect the liver so it is recommended that you have regular blood tests to monitor liver function every two weeks for the first three

months then monthly after that. Sometimes the dose of abiraterone needs to be reduced. All hormone treatments for prostate cancer can cause osteoporosis with an increased risk of fractures.

Clinical trial outcomes

There are two key trials of abiraterone in men with metastatic castrate-resistant prostate cancer: COU-AA-301 in men who had been treated with docetaxel and COU-AA-302 in men who were chemotherapy naïve. It is important to note that in both trials abiraterone plus prednisolone was compared to prednisolone alone not to a placebo. Prednisolone is known to have anti-cancer effects in prostate cancer. Post-docetaxel COU-AA-301 showed that abiraterone improved median overall survival from 11.2 to 15.8 months and median radiological progression-free survival from 3.6 to 5.6 months. In men who had never received chemotherapy COU-AA-301 showed that abiraterone improved median overall survival from 30.3 to 34.7 months and significantly improved radiological progression-free survival^{68,69}.

Enzalutamide

What it is and who's suitable?

Enzalutamide can be used to treat men whose prostate cancer has spread beyond the prostate and who have had previous treatment with hormone injections (goserelin, leuprorelin, triptorelin or degarelix). It can be given either before or after chemotherapy with docetaxel if this is being considered. Some men cannot be treated with chemotherapy.

Benefits to patients

Enzalutamide prolongs survival of men with metastatic castrate-resistant prostate cancer by about four to five months whether it is given before or after chemotherapy^{72,73}.

Support for men to ensure quality of life

The most common side effects with enzalutamide are tiredness, hot flushes, headache, memory impairment and a rise in blood pressure. It is important to measure blood pressure regularly.

All hormone treatments for prostate cancer can cause osteoporosis with an increased risk of fractures.

Clinical trial outcomes

There are two key trials of enzalutamide in men with metastatic castrate-resistant prostate cancer: the AFFIRM study of enzalutamide versus placebo in men who had been previously treated with docetaxel chemotherapy and the PREVAIL study in men who were chemotherapy naïve. After chemotherapy enzalutamide improved median survival from 13.6 to 18.4 months and median radiological progression-free survival from 2.9 to 8.3 months. Pre-chemotherapy, enzalutamide improved median overall survival from 31.3 to 35.3 months and median radiological progression-free survival from 5.4 to 20 months. The duration of treatment was 18.2 months for enzalutamide and 5.4 months for placebo.^{71,72}

Abiraterone vs enzalutamide

As there is little or no evidence to support recommendations for stratification or sequencing of second line hormone treatments, the choice between abiraterone and enzalutamide is subjective, but should also take account of the side-effects especially in relation to co-morbidities.

We have patient information on second line hormone therapy in [print](#) and [online](#)

2.9 Chemotherapy

What it is and who's suitable?

Chemotherapy, or cytotoxic chemotherapy, is a term generally used to describe drugs which work by killing cancer cells by disrupting the process of cell division, one of the hallmarks of cancer. Relatively few chemotherapy drugs are used in the treatment of prostate cancer, and, in the initial stages of treatment, the only such drug in routine use is docetaxel.

For men with metastatic prostate cancer where initial hormone therapy (ADT) is no longer controlling the disease (sometimes referred to as 'metastatic castration resistant prostate cancer' or mCRPC), docetaxel in combination with oral prednisolone⁸ is a treatment option for men who have not previously received docetaxel. In this situation, up to 10 cycles are administered if the treatment is working and if the side effects are tolerable.

Docetaxel was initially used only in men with metastatic prostate cancer where initial hormone therapy had stopped working. However, in 2016, the results of the UK STAMPEDE trial⁶⁵ demonstrated that the use of docetaxel at the time of initiation of androgen deprivation therapy significantly increased overall survival for men with metastatic or high risk, locally-advanced disease. Docetaxel is given once every three weeks by intravenous infusion over one hour for six cycles in this situation⁶⁶.

Arm H of the Stampede trial⁸⁷ found that radiotherapy to the prostate improved overall survival in men with a low metastatic burden. Three-year overall survival for men who were given radiotherapy targeted to their prostate (intervention) was 81% compared to men who just receiving ADT and/or docetaxel (standard) which was 73%. This increase in overall survival is significantly significant. The definition used for low metastatic burden is patients who do not have ≥ 4 metastases, including 1 outside the pelvis & spine or visceral metastases. Currently there are no clinically significant results to determine whether the patients with low metastatic burden should have radiotherapy targeted to the prostate before or after chemotherapy.

Evidence also supports the use of docetaxel in combination with hormone therapy – and with or without external beam radiotherapy – as a treatment option for men with hormone-naïve, high-risk locally advanced prostate cancer.

Results from the meta-analysis accompanying the STAMPEDE trial data shows that offering docetaxel to men at this stage of the disease who are receiving long-term hormone treatment with or without radiotherapy, significantly reduced treatment failures, from 30% to 22% at four years⁷⁵. In addition, the control arm of the STAMPEDE trial showed progression to occur in about 72% of men after 5 years compared with about 62% with the addition of docetaxel⁶⁶. This includes men with metastatic and non-metastatic prostate cancer. A similar benefit for docetaxel was seen in both groups; the hazard ratio for failure-free survival was 0.60 (95% CI 0.45-0.80) in men with non-metastatic disease, and 0.61 (95% CI 0.53-0.71) for men with metastatic disease. Men having standard treatment without the addition of docetaxel progress more quickly to hormone-refractory disease (median 15 months' difference)⁶⁶.

High-risk locally advanced disease is defined by the STAMPEDE trial as locally-advanced prostate cancer with at least two of: T3/4 disease, Gleason score of 8–10, and prostate-specific antigen ≥ 40 ng/ml⁶⁶. Patients should be of sufficient performance status to be treated with 6 cycles of docetaxel chemotherapy, with no clinically significant cardiovascular history.

Docetaxel is not suitable for all men with metastatic prostate cancer. Its side effect profile is such that men with poor performance status (3 or worse), extensive comorbidity or some specific comorbidities (such as pre-existing peripheral neuropathy) will be considered at unduly high risk of serious complications or death from toxicity, and so, in these men, this docetaxel is best avoided⁷⁴.

Cabazitaxel, which is licensed for use in men with metastatic prostate cancer where initial hormone treatment has stopped working, is currently reserved for men who have previously received docetaxel and so it not likely to be used as a first treatment⁷⁵.

Cabazitaxel is a similar drug to docetaxel, but is specifically designed to overcome the cancer's ability to resist the effects of docetaxel. Its use is therefore reserved for men who have previously received docetaxel and it has been shown to improve overall survival and pain control in such men when compared to mitoxantrone⁷⁶. Cabazitaxel is also given in combination with oral prednisolone and is also given as three-weekly one-hour infusions for up to 10 cycles.

The safety and benefits of further docetaxel in men who previously received docetaxel at the time of initial ADT is not clear, although this may be a reasonable option for some men where cabazitaxel is contraindicated or not available.

Mitoxantrone, though not licensed in prostate cancer in the UK, is occasionally offered. It is not proven to improve survival⁷⁷, but has been shown to improve symptom control. Its use is therefore restricted to men who are not suitable for docetaxel or cabazitaxel (perhaps due to prior exposure to these drugs) who have symptoms. It is given as an intravenous injection once every three weeks for up to 10 cycles and is given with daily prednisolone. Unlike docetaxel and cabazitaxel, mitoxantrone is contraindicated in men with significant heart conditions.

Benefits to patients

When used alongside ADT at the time of initial diagnosis in men with metastatic disease, docetaxel has been shown to prolong survival (by, on average, in excess of one year) and significantly delay deterioration in the cancer (increasing PSA, worsening of scans and / or worsening of symptoms)⁶⁵.

When used alongside prednisolone in men where initial ADT has stopped controlling the disease, docetaxel can improve survival (by, on average, around three months) and delay the deterioration of the disease⁶⁵. In men with symptoms such as pain, docetaxel may bring about some improvement.

Cabazitaxel when used alongside prednisolone in men where initial ADT and prior docetaxel has stopped controlling the disease can improve survival (by, on average, around 2.5 months) and delay deterioration of the disease. It can also improve symptoms⁷⁶.

The main side effects of docetaxel or cabazitaxel are:

- fatigue
- hair loss (which is not universal)
- diarrhoea
- nausea (rarely vomiting, if anti-sickness drugs are used)
- neutropenia (low white blood cells) associated with fever and / or infection
- nerve damage (tingling and / or numbness in toes and / or fingers, rarely weakness of the legs)
- allergic reaction (which, if it occurs, will occur during the infusion)
- heart rhythm problems
- fluid retention.

Not all men will get all or any of these side effects and there are other rarer side effects which can occur.

For men with metastatic prostate cancer which is no longer controlled by initial ADT, other treatments may be used before docetaxel. Abiraterone and enzalutamide have been shown to be effective in men who do not have significant symptoms in this context. Similarly Radium-223 can be effective in men with bone symptoms who have not yet received docetaxel⁷⁸. For men who could potentially receive two or more of these treatments, it is not known which sequence of treatments will result in the best overall results, and so it is important that these men are offered a choice of treatments to help them choose which treatment is best for them at that point in their life.

Support for men to ensure quality of life

The side effects of chemotherapy vary from one man to another and it is usually impossible to predict who will suffer which side effects. Steps can be taken to avoid certain side effects. For example, most men will receive high doses of corticosteroids (usually dexamethasone) immediately prior to each dose of docetaxel to prevent fluid retention and allergic reactions.

Most men will receive preventative anti-sickness medicines immediately before and often for a few days after each dose of chemotherapy.

Other side effects are harder to predict or prevent and it is essential that the individual patient's side effects from the previous cycle are assessed before each new dose of chemotherapy. Sometimes additional measures are required to prevent recurrence (for example changing or increasing anti-sickness medicines).

Sometimes it is necessary to reduce the dose of chemotherapy to prevent recurrence (for example where there has been infection or fever associated with neutropenia). Occasionally additional drugs called growth factors may be offered to prevent recurrent infection or fever associated with neutropenia. Sometimes these growth factors are given even when there has not been previous infection, fever or neutropenia (i.e. with the first dose of chemotherapy).

Patients often ask if they need to modify their activities during chemotherapy. By and large patients are encouraged to continue life as normal as far as possible during chemotherapy. In particular, many men seek reassurance that it is safe to continue to have regular contact with friends and family both young and old whilst they are receiving chemotherapy. Exercise during chemotherapy should not be discouraged, although men may find there are some days where their physical energy levels are such that their ability to exercise is impaired. Usually these energy levels will recover within a few days. There is no good evidence that change in diet will affect the outcomes of chemotherapy, although some men do find that their sense of taste is affected by the treatment.

Chemotherapy, regrettably, does not offer a cure in prostate cancer, so it is important that a man's quality of life is assessed regularly during chemotherapy: if the side effects are having a significant impact on quality of life it may not be appropriate to continue the chemotherapy and alternatives should be considered.

We have patient information about chemotherapy in [print](#) and [online](#).

3.0 Treatment for bone metastases

Men with prostate cancer that has metastasised to their bones may benefit from bone targeted therapies such as bisphosphonates, strontium-89 and radium-223 dichloride. These may be given as treatment for symptomatic bone metastases or to suppress the metastases.

However, NICE recommends that bisphosphonates, which are used to treat cancer-related hypercalcaemia and osteoporosis caused by androgen deprivation, should not be given to men with hormone-relapsed prostate cancer to prevent or reduce the complications of bone metastases⁸. They should instead be given for pain relief when all other treatments have failed.

NICE guidelines⁸ also point to the use of strontium-89, which is a beta-emitting radioactive isotope given intravenously. It has been shown to improve pain control, and prevent new sites of pain, but should not be given to men with hormone-relapsed prostate cancer who are likely to receive myelosuppressive chemotherapy. Strontium-89 can cause side-effects that include flushing and an increase in bone pain, as well as more adverse side-effects that include⁷⁹:

- black, tarry stools
- blood in urine or stools
- cough or hoarseness
- fever or chills
- lower back or side pain
- painful or difficult urination
- pinpoint red spots on skin
- unusual bleeding or bruising.

More recently, a new radioisotope called radium-223 dichloride has achieved approval for use in routine commissioning for men who have undergone hormone therapy and chemotherapy in the form of docetaxel^{78,80}. Radium-223 is indicated for use in men with castrate-resistant prostate cancer with symptomatic bone metastases and no known visceral metastases⁸¹ It is suitable for men who have not yet

undergone chemotherapy but have stopped responding to hormone therapy and has been approved for use before chemotherapy in England, Scotland and Wales. It remains under review for this indication in Northern Ireland.

Radium-223 is a radiopharmaceutical (a drug which contains a radioactive substance) which is administered intravenously usually in six cycles at four weekly intervals. It is designed to target bony metastases by delivering a controlled dose of radiation to cancer cells without affecting normal bone marrow or surrounding tissue. For this reason, there are specific treatment delivery requirements for radium-223. Services are required to have an Administration of Radioactive Substances Advisory Committee (ARSAC) license and Environment Agency approval in order to deliver treatment with radionuclides.

It should also be delivered in an appropriate facility, within designated areas for therapy handling and administration of radionuclides, with provision for outpatient therapies to be administered in a specified location⁸². Delivery of inpatient molecular radiotherapy and subsequent care of radioactive inpatients should be undertaken in an appropriately designated room^{83,84}.

Staff involved in caring for the patient should be familiar with radiation protection and with the condition being treated⁸². The doctor prescribing treatment carries responsibility for the delivery of molecular radiotherapy and for any complications arising from that treatment; follow-up may be undertaken by this clinician (such as the ARSAC certificate holder) or by the referring clinician⁸².

It is important that the following conditions are given consideration prior to commencing or resuming treatment with radium-223;

- bone fractures
- established or imminent spinal cord compression
- crohn's disease or ulcerative colitis
- bone marrow suppression
- osteonecrosis of the jaw
- secondary malignant neoplasms.

Radium-223 is generally well tolerated but can have the following side effects⁸⁵;

System Organ Class (MedDRA)	Very common	Common	Uncommon
Blood and lymphatic system disorders	Thrombocytopenia	Neutopenia Pancytopenia Leukopenia	Lymphopenia
Gastrointestinal disorders	Diarrhoea Vomiting Nausea		
General disorders and administration site conditions		Injection site reactions	

Men should be fully counselled about these side effects so that they can demonstrate a clear understanding of the risks associated with them. This should take place before consenting to treatment with radium-223. Written and oral information should be provided as per the NICE Clinical Guidance for Improving Patient Experience in Adult Services (CG138)².

We have patient information on bisphosphonates ([print](#) and [online](#)) and radiotherapy for advanced prostate cancer ([print](#) and [online](#))

3.1 Metastatic spinal cord compression

Metastatic spinal cord compression (MSCC) occurs when bone metastases place direct pressure on the nerves in the spine. In some cases, this can cause damage to the spine and can lead to permanent paralysis.

While MSCC can be rare, it's potential to result in paralysis makes it critical that action is taken on the following systems, especially if the patient has been diagnosed with secondary bone metastases:

- Pain or soreness in the lower, middle or upper back or neck that is severe or different from usual pain. The pain might get worse when the patient coughs, sneezes, lifts or strains, or goes to the toilet. It might get worse when the patient is lying down. It may wake the patient at night or stop him from sleeping.
- A narrow band of pain around the stomach or chest that can move towards the lower back, buttocks or legs.
- Pain that moves down the arms or legs.
- Weakness in arms or legs, or difficulty standing or walking. The patient might feel unsteady on his feet or feel as if his legs are giving way. Some men say they feel clumsy.
- Numbness or tingling (pins and needles) in legs, arms, fingers, toes, buttocks, stomach area or chest, that doesn't go away.
- Problems with bladder or bowel control or difficulty emptying the bladder or bowel.

These symptoms can of course also be caused by other conditions, but it is still important that men are treated with suspicion of MSCC and are referred immediately to Accident and Emergency.

NICE has developed a Quality Standard that makes sure effective processes are in place for the early detection, diagnosis and management of metastatic spinal cord compression (MSCC) in adults (18 years and older)⁸⁶. The seven statements that make up this Quality Standard are as follows:

Statement 1.

Adults at high risk of developing metastatic spinal cord compression (MSCC), and their families or carers (as appropriate), are given information that describes the symptoms of MSCC and what to do if they develop symptoms.

Statement 2.

Adults with spinal pain suggestive of spinal metastases, but with no neurological symptoms or signs, have an MRI of the whole spine and any necessary treatment plan agreed within one week of the suspected diagnosis.

Statement 3.

Adults with suspected MSCC who present with neurological symptoms or signs have an MRI of the whole spine and any necessary treatment plan agreed within 24 hours of the suspected diagnosis.

Statement 4.

Adults with suspected MSCC who present with neurological symptoms or signs have their diagnostic investigations coordinated by an MSCC coordinator.

Statement 5.

Adults with MSCC have their ongoing care coordinated by an MSCC coordinator.

Statement 6.

Adults with MSCC, who present with neurological symptoms or signs, start definitive treatment (if appropriate) within 24 hours of the confirmed diagnosis.

[Statement 7.](#)

Adults with MSCC have a management plan that includes an assessment of ongoing care and rehabilitation needs.

We have patient information on MSCC to [print](#) and read [online](#)

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