

Prostate cancer

There are multiple treatment options for patients with low-risk prostate cancer: active surveillance, surgery, external beam radiotherapy and low-dose rate brachytherapy. There is no evidence to suggest a difference in survival outcomes for the various options. Therefore, patients must take into account the advantages and disadvantages of each treatment including the logistics, side effects and risks. Although doctors should provide information and advice, the patient must ultimately make their own informed decision. This can be incredibly difficult.

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In the UK, prostate cancer is the most common cancer occurring in men.¹ Age is the strongest known risk factor for prostate cancer, with 75% of cases occurring in men over 65 years of age.

Although UK incidence of prostate cancer has been rising, this has not been reflected by a change in mortality rates. This is likely to be attributed to increased use of prostate specific antigen (PSA) testing, leading to identification of more men with low risk tumours.^{2,3} Many of these patients will die whilst suffering from prostate cancer, rather than dying of the prostate cancer itself.⁴ This raises important questions about the cost and quality of life with the treatment of this low risk subgroup.

The article will emphasise the challenging, yet crucial decision-making process that these patients face when choosing a treatment. It will explain the advantages and disadvantages of each treatment option, and how these can aid the patient in the important task of making an informed decision. This process is unique to these particular men as decisions must take into account, amongst other elements, the patient's comorbidities, personal situation and beliefs.

Prostate tumour assessment

Risk stratification for prostate cancer involves three main criteria: Prostate Specific Antigen (PSA), Gleason Grading and TNM staging. Only once these criteria have

been reviewed can the multidisciplinary team offer the patient the treatment options appropriate for their particular cancer.

PSA

PSA is a protein produced by normal cells in the prostate gland. Damaged prostate cells can lead to increased levels of PSA, which may be an indicator of prostate cancer. However, elevated PSA levels are also seen in conditions such as benign prostatic hyperplasia and prostatitis. Furthermore, PSA values will increase with age. Therefore, the most helpful measurement of PSA is a trend over time, taking into account doubling time, rather than an absolute figure. An elevated PSA value is not diagnostic of prostate cancer, but rather an indication of whether biopsy is appropriate.

Gleason score

Once a biopsy has been performed the specimen is graded using the Gleason System. The system scores the predominant and second most dominant cellular patterns between 1–5 according to differentiation from the tissue of origin. These two grades are added together to give an overall score between 2–10. The higher the number, the more aggressive the cancer.

TNM staging

TNM staging assesses the dimensions and location of

Box 1: Risk Stratification for men with localised prostate cancer⁵

	PSA		Gleason score		Clinical stage
Low risk	<10ng/ml	and	≤6	and	T1–T2α
Intermediate risk	10–20ng/ml	or	7	or	T2b–T2c
High risk	>20ng/ml	or	8–10	or	T3–T4

the primary tumour (T), describes if, which and how many lymph nodes are involved (N), and whether metastases are present (M).

Treatment options for low grade prostate cancer

There are four main treatment options available for low risk prostate cancer: active surveillance, surgery (radical prostatectomy), external beam radiotherapy and low-dose rate brachytherapy. Some factors will rule out one or more of these options, for example a patient unfit for general anaesthetic would be unsuitable for surgery or brachytherapy. However, a large number of patients are clinically referred to as "suitable for all options", meaning it will be their decision as to which treatment they prefer. Under these circumstances, patient-orientated factors become more important.

Current research suggests that surgery, external beam radiotherapy and low-dose rate brachytherapy all have equal survival outcomes when treating low-risk prostate cancer.⁶ Since there is no survival benefit for any treatment, the patient has a very difficult decision, and one that many patients do not wish to make themselves. However, the clinical team aim to provide all information in an unbiased way, explaining all of the risks and benefits of each option in order to help the patient make an informed choice.

Active surveillance/watchful waiting

Routine PSA testing has led to a large number of patients diagnosed with prostate cancer, in whom the disease would not become symptomatic or affect their survival rate.⁷ In fact 80% of men over 80 years will have some form of neoplastic change in the prostate.⁸ Many of these patients will die with the prostate cancer, rather than of the prostate cancer itself. In these patients, active surveillance could

prevent the unnecessary debilitating side effects of treatment such as impotence and incontinence, without compromising survival.

NICE guidance recommends active surveillance as the treatment of choice for men with T1c, Gleason score of 3+3, PSA density of <1.5ng/ml, who have cancer in less than 50% of their biopsy cores, with <10mm of any core involved. Men who are candidates for active surveillance should have a minimum of 10 biopsy cores taken to reduce sampling error.⁹

Patients who choose the option of active surveillance are monitored closely by testing serum PSA levels and repeating prostate biopsies. Results of these tests provide evidence supporting the continuation of the active surveillance programme or proceeding to curative treatment. Biopsies can be painful, cause bleeding and run the risk of infection, but radical treatments may have a much larger negative impact on quality of life.

One disadvantage with active surveillance is that patients may suffer from psychological distress as they have a cancer that is not being treated. However recent research has found that depression did not correlate with patients on active surveillance versus curative treatments.¹⁰

The method of active surveillance also enhances research opportunities, providing the opportunity of further understanding the natural history of prostate cancer. A trial called PROACTIV at the Royal Marsden is currently under development and aims to gain insight into the effect of nutrition on prostate cancer progression using patients under active surveillance.¹¹ Studies of this kind may lead to the risk reduction of prostate cancer.

There is overwhelming evidence supporting the option of active surveillance, however, some patients find it difficult to live with a diagnosis of cancer and choose curative treatment. Men who have chosen an active surveillance programme who show signs of disease progression (a rise in PSA levels, or adverse findings on biopsy) or change their mind are offered radical therapy

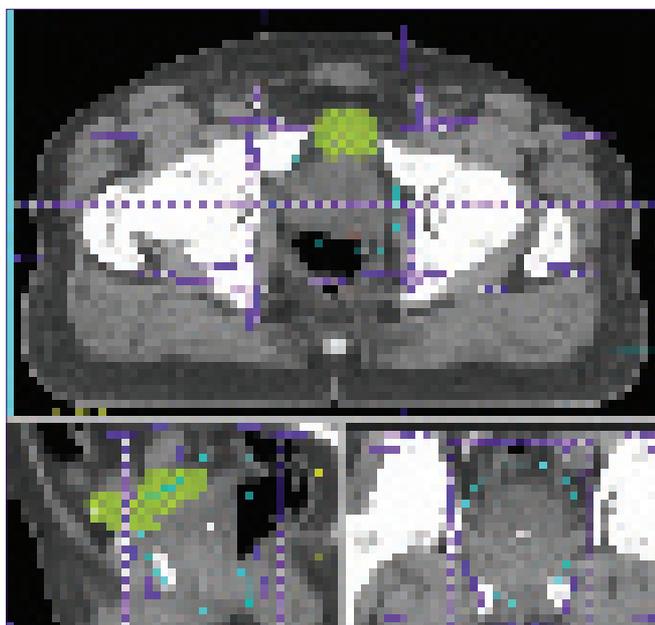


Figure 1: 3-dimensional radiotherapy plan showing prostate planning target volume (blue), bladder (yellow) and radiotherapy fields (purple)

taking into account the patient's comorbidities, life expectancy and choice.

Watchful waiting is the term used to refer to the monitoring of patients using PSA alone. Often these patients have multiple comorbidities and would not be suitable for radical intervention. In this case, patients are treated expectantly using medical hormonal manipulation if they become symptomatic or if the PSA doubling time is short.

Surgery (radical prostatectomy)

Radical prostatectomy aims to remove the entire prostate whilst the disease is organ confined. This operation can either be performed through a retropubic or perineal incision. Urologists can perform different techniques to excise the prostate and lymph nodes; either open or laparoscopic, and at some specialist centres, robotic surgery is now being offered. Newer methods may have fewer potential complications and reduce post-operative in-patient stay.

Some patients have an overwhelming instinct to have the affected organ removed completely. This is the advantage of surgery. In addition, one operation may be more suitable for some patients rather than a treatment such as external beam radiotherapy, which requires daily visits to hospital for a period of weeks.

Radical prostatectomy is unsuitable for many elderly patients in view of multiple comorbidities. In particular, a general anaesthetic may be inappropriate with a potential higher risk of complications. Post-operative care may require in-patient stay of up to a week, which may be the deciding factor for some men.

If patients do undergo radical prostatectomy, recurrence in the prostate bed is seen in 33% of cases.¹² Furthermore, impotence occurs in 50% of men under the age of 60 years who have had nerve sparing prostatectomy, increasing up to 80% of men over the age of 70 years who have not had nerve sparing surgery.¹² In addition most men may have some level of incontinence following surgery but this usually improves over time. Other side effects include diarrhoea or constipation for a few months following the operation.

External beam radiotherapy

Radiation therapy damages deoxyribonucleic acid (DNA) within affected cells so that they cannot replicate and eventually undergo apoptosis. Conformal radiotherapy is given by a linear accelerator that uses shaped megavoltage x-rays to target the affected area.

Radiotherapy planning begins with a CT scan of the patient in the treatment position. This allows the radiotherapy to be planned. As the plan requires precise positioning of the patient, the patient has three permanent tattoos in the mid line and laterally to ensure that they are in exactly the same position for every treatment ensuring the radiotherapy is delivered as planned.

The area of the prostate that requires treatment is marked out on each slice of the CT scan, and margins are added that allow for movement of the patient during treatment and potential microscopic disease.

To limit the radiation to normal tissue, multi-leaf collimators (MLC) are used to conform the shape of the beam. This reduces the dose of radiotherapy to normal tissues and limits toxicity. NICE guidance recommends the dose of radiation to be 74Gy in 37 fractions over 7 1/2 weeks.⁵ Figure 1 shows a three-dimensional external beam radiotherapy plan.

External beam radiotherapy is reasonably well tolerated in older men, delivered consecutive weekdays on an outpatient basis. However, patients do travel daily to hospital to complete the full course of treatment. Many patients may have to travel a significant distance to their specialist cancer centre, which may cause logistical problems.

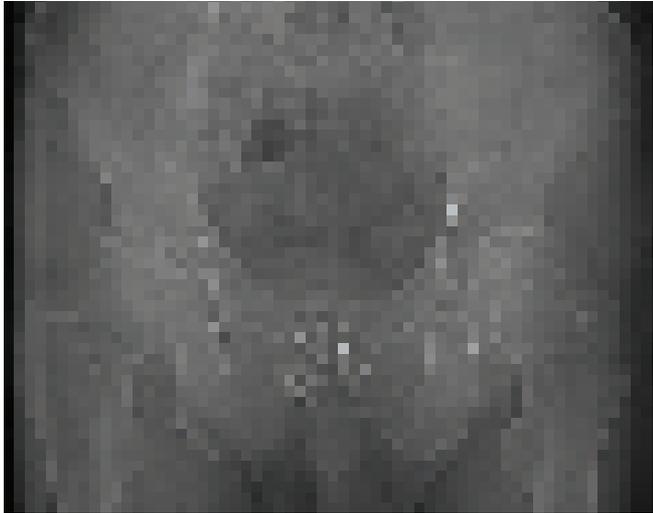


Figure 2: Plain X-ray of pelvis demonstrating iodine seeds used in low dose rate brachytherapy

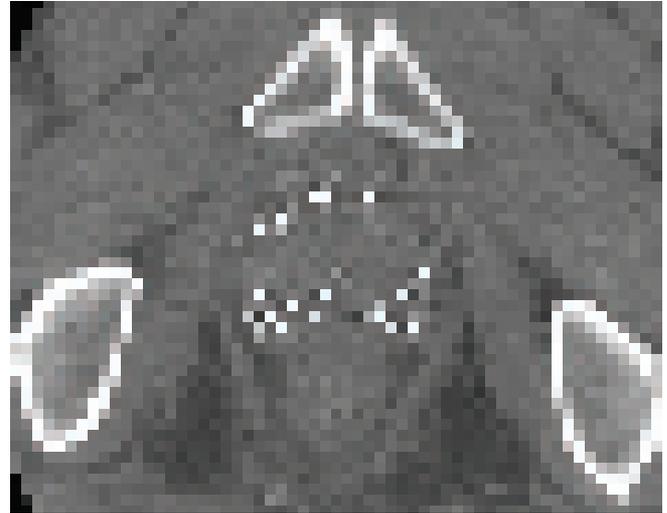


Figure 3: Axial CT slice through pelvis demonstrating iodine seeds used in low dose rate brachytherapy

The main side effects of external beam radiotherapy usually begin approximately 2 weeks into treatment and resolve approximately 6–8 weeks after completion of treatment. They include tiredness, lethargy and "sunburn-like" irritation to the area being treated. The radiation field will encompass some of the bladder and rectum due to their proximity to the prostate gland, therefore, patients may experience increased urinary and bowel frequency, and urgency as well as dysuria, proctitis, tenesmus, bleeding per urethra/per rectum, diarrhoea and passing mucus from the rectum. Side effects can be improved with increased fluid intake, particularly cranberry juice for dysuria and by taking Fybogel or Isogel to regulate bowel habit. External beam radiotherapy has a 30–40% risk of impotence, however, this is lower than with radical prostatectomy.¹³ Due to scarring there is also a very small risk of future bowel or bladder surgery due to late toxicity. External beam radiotherapy may be unsuitable for patients with bowel disease such as ulcerative colitis, Crohn's or diverticulitis.

It must also be emphasised to the patient that external beam radiotherapy will not improve lower urinary tract symptoms.

Brachytherapy

Low-dose rate (LDR) brachytherapy involves insertion of radioactive iodine (I125) seeds directly into the prostate gland, where they remain, emitting low level radiation for approximately one year after implantation. The seeds deliver a high dose of radiation directly to the prostate. The surrounding tissues receive less radiation resulting in fewer

side effects.

The procedure only requires two visits to hospital rather than the daily visits required for External Beam Radiotherapy. However both visits require a general anaesthetic, which may be contraindicated in some patients. Furthermore, brachytherapy is not suitable for patients with a prostate gland larger than 50–60cc in volume, who have had a previous transurethral resection of the prostate (TURP), or have a high international prostate symptom score (IPSS).

The first visit involves a trans-rectal ultrasound in theatre assessing the volume and location of the prostate gland in relation to the pubic arch to see if brachytherapy is logistically possible. If possible, the radiotherapist and physicist plan the treatment calculating the number and localisation of the seed implants to ensure adequate delivery of radiotherapy to the prostate.

The second visit is for implantation of the radioactive seeds. Due to meticulous planning the seeds can be positioned with a high degree of accuracy. Approximately 80 seeds are implanted through fine needles inserted into the perineum by ultrasound guidance. Each seed is 4.5mm in length and 0.8mm thick. Figures 2 and 3 show the location of the iodine seeds used in low dose rate brachytherapy.

As two general anaesthetics are required for brachytherapy (one for the volume study and the second for the seed implantation), patients must be suitable anaesthetic candidates.

Brachytherapy tends to cause more urinary symptoms, but fewer bowel symptoms when compared with external

beam radiotherapy. Side effects include: frequency and urgency of micturition, poor flow, dysuria, haematuria and discomfort. About 10–15% of men may get acute retention of urine and require a catheter. Longer-term side effects include impotence in 40–50% of men under the age of 60 years, reduction in ejaculate volume, a small chance (<2%) of incontinence and rarely (<1%) chronic proctitis.¹³

Conclusion

Elderly patients diagnosed with low-risk prostate cancer have a challenging decision to make regarding choice of treatment option. Some patients have disease orientated factors rendering them unsuitable for certain options, for example patients with prostate glands >50–60cc are unsuitable for brachytherapy. Yet increasingly, patients have multiple treatment options available to them.

Evidence shows that all treatments have an equal effect on survival rate for cancer. Therefore, it is imperative that patients understand all aspects of each treatment option available to them via discussions with healthcare professionals and access to relevant literature. This should include information on treatment regimens, acute and long-term side effects and potential risks. Patients should be encouraged to ask questions and explore their concerns. As these cancers are defined as low risk, patients have ample time to evaluate their needs and resources to cope. Many patients will choose to discuss this with friends and family, their GP and specialist nurses. There is also the option to join a prostate cancer support group in order to meet other men who have undergone similar decision-making processes.

The role of the specialist doctor (urologist and oncologist) is to discuss the pros and cons of each treatment, but only the patient themselves can make a decision as to the risks they are willing to take, what side effects they can tolerate and what compromises they can accept.

Due to a growing ageing population, a greater number of elderly men will face this dilemma, if the predicted trend of increasing incidence of low risk prostate cancer continues. Currently "experimental" treatments such as cryosurgery or high frequency ultrasound (HIFU) are not standard options. The future will inevitably lead to increasing numbers of men facing ever more complex decisions with regard to their treatment.

Conflict of interest: none declared

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