Treatment modalities for localised prostate cancer

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There are often several suitable treatment options for any individual patient with localised prostate cancer. The authors clarify some of the issues involved when helping men to face the difficult treatment decision of how best to manage their disease.

Prostate cancer is the most common cancer in men, with about 36,000 men diagnosed each year in the UK. With increasing awareness of the disease leading to greater uptake of the prostate-specific antigen (PSA) test coupled with a digital rectal examination (DRE), the cohort of patients with localised prostate cancer is growing.

Those with a strong family history (multiple first-degree relative involved) or racial predisposition are particularly at risk. African and Caribbean men have a far higher incidence of prostate cancer and often present later in clinical stage with more aggressive disease. In spite of this, in many cases, prostate cancer is slow-growing with no symptoms, and many of the patients eventually die of other causes, unrelated to the cancer.

Unlike with most other solid organ tumours, there are often several suitable treatment options for any individual patient with localised prostate cancer, and there is usually enough time to make a
considered choice. Many men face this difficult treatment decision of how best to manage their disease and often turn to their GP or other members of the primary care team for advice. Individual clinicians often offer their own chosen treatment modality first, and patients face considerable difficulty in weighing up the advantages of each treatment option.

**DIAGNOSIS OF PROSTATE CANCER**

As localised prostate cancer is usually an asymptomatic disease, it is often diagnosed incidentally by an elevated PSA noticed during a routine check-up. Adenocarcinoma of the prostate preferentially occurs in the peripheral zone of the prostate and therefore needs to be of significant size to cause symptoms.

Occasionally, localised prostate cancer can be symptomatic, often with voiding or storage symptoms similar to benign prostatic hyperplasia, including prolonged voiding, hesitancy, incomplete emptying, frequency, nocturia, haematuria and dysuria.

By contrast, advanced prostate cancer causes general and metastatic manifestations such as weight loss and loss of appetite, anaemia, bone marrow suppression, bone pain, pathologic fracture, spinal cord compression, and oedema caused by obstruction of venous and lymphatic tributaries by nodal metastasis.

Uraemic symptoms can occur from ureteral obstruction caused by local prostate growth or retroperitoneal adenopathy secondary to nodal metastasis.

Suspected prostate cancer in patients who present with elevated PSA levels or abnormal DRE findings is typically confirmed by a 12-core transrectal needle biopsy of the prostate. Further tests, such as magnetic resonance imaging (MRI) and bone scans, may be performed to determine whether prostate cancer has spread.

**MANAGEMENT OF LOCALISED PROSTATE CANCER**

The treatment decision for an individual man with localised prostate cancer depends on a number of key factors in each case:

- the patient’s overall life expectancy, as determined by age and comorbidities
- the biological characteristics of the tumour, including Gleason grade, number of biopsy cores positive for cancer, the actual percentage of core involvement, and the clinical and radiological stage
- the preferences of the patient for the various treatment options, with consideration of complications, adverse effects, relative efficacy, and quality-of-life issues
- previous surgery or radiotherapy to the abdomen/pelvis
- the desire or perceived potential need for salvage treatments
- the availability of various treatments in the region.

Localised prostate cancer includes tumours that are clinically localised and appear to be organ confined based on available imaging. These tumours are also referred to as T1 and T2 within the TNM staging system, but may include some pathological T3 tumours.

To aid decision-making, men with localised prostate cancer are stratified into risk groups according to their risk of recurrence and overall survival. A multidisciplinary team discussion should assign a risk category to all newly diagnosed men with localised prostate cancer (Table 1). Men with low-risk disease are managed with either radical treatments (surgery, radiation therapy or brachytherapy) or conservative approaches (watchful waiting or active surveillance).

**RADICAL TREATMENT OPTIONS**

Radical treatment options include radical prostatectomy (RP), external beam radiation therapy (EBRT) and brachytherapy.

**Radical prostatectomy**

The surgical removal of the prostate and seminal vesicles is one of the gold-standard treatments for intermediate- to high-risk disease. There are now three common approaches to performing RP: retropubic, laparoscopic and robotic. Perineal prostatectomy is also still performed in some centres.

The laparoscopic and robotic techniques are becoming more frequently adopted, as they have the advantages of reduced blood loss, reduced pain, shorter inpatient stays and convalescence when compared to the open approach. High-volume centres performing these approaches report excellent results with regard to oncological and functional outcomes, but there is a lack of level 1 evidence to support their use. It is likely that robotic prostatectomy using the da Vinci surgical system will be the most common technique in the UK within the next few years (see Figure 1).

According to the British Association of Urological Surgeons, patients selected for surgery should have anaesthetic fitness, at least 10 years’ life expectancy, and preferably be under the age of 70.
However, there is no age threshold for RP and a patient should not be denied this procedure on the grounds of chronological age alone, but on the existence of comorbidities, for they may greatly increase the risk of dying from non-prostate cancer-related causes. Relative contraindications include previous significant abdominal surgery and bleeding diatheses.

The goal of RP by any approach is total eradication of disease, while preserving continence and, whenever possible, potency. There is increased interest among the urological community for the treatment of high-risk disease with RP coupled with an extended pelvic lymphadenectomy. This is partly because of the much lower morbidity seen with the current minimally invasive techniques and partly as a result of the improvements in salvage radiotherapy to the prostatic bed for those in whom cure is not primarily achieved. European Association of Urology (EAU) guidelines and recommendations for RP are summarised in Box 1.

**External beam radiation therapy**

This involves treating the prostate with around 74Gy of radiation in divided fractions over a six- to seven-week course. Depending on whether the disease is low, intermediate or high risk, neoadjuvant (three months) or adjuvant (2.5 years) hormonal therapy is given concurrently. This usually takes the form of a luteinising hormone-releasing hormone agonist or anti-androgen medication.

Computed tomography and MRI scans are used to define target areas and plan the administration of radiotherapy. Intensity-modulated radiation therapy allows for modulation of the dose intensity to target the cancer. Recent advances include the use of radio-opaque markers to delineate the extent/location of the cancer.

External irradiation offers the same long-term survival results as surgery; in addition, EBRT provides a quality of life at least as good as that provided by surgery.

In terms of patient selection, EBRT is commonly used in the treatment of older patients (>65 years) who have a greater likelihood of metastatic disease, or those who decide against surgical intervention. Indications for definitive radiation therapy are summarised in the EAU guidelines.

External beam radiation therapy may be unsuitable for patients with bilateral hip replacements, previous radiotherapy to the same region (pelvic radiotherapy for seminoma, or colorectal tumours), severe proctitis or bowel morbidity, including ulcerative colitis and diverticular disease, as well as poorly controlled diabetes. Patients should ideally be uncatheterised, able to hold a moderate volume of urine in the bladder and able to lie still.

**Brachytherapy**

Low-dose transperineal prostate brachytherapy involves the placement of small radioactive ‘seeds’ into the prostate under a general anaesthetic (Figure 2). It may be carried out in one or two stages by a combination of urologists and clinical oncologists. After mapping the prostate for extent and position, 80–100 seeds of iodine-125 or caesium-137 are placed, ensuring uniform coverage of the prostate and a margin around it, with the urethral area generally spared. The seeds are permanently placed; early side-effects include urinary retention, haematuria and infection.

There is generally a lower morbidity with brachytherapy than with RP or EBRT, but side-effects include worsening of storage lower urinary tract symptoms, faecal urgency, rectal symptoms, sexual dysfunction, urethral strictures and treatment failure. Overall it is a safe and effective curative technique that generally requires fewer than two days of hospitalisation. It is usually recommended for:

- Gleason score ≤6
- Initial PSA level <10ng/ml

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**BOX 1. Guidelines and recommendations for radical prostatectomy**

**INDICATIONS**

- In patients with low- and intermediate-risk localised prostate cancer (T1a–T2b and Gleason score 2–7 and PSA ≤20ng/ml) and a life expectancy >10 years

**OPTIONAL**

- Patients with stage T1a disease and a life expectancy >15 years or Gleason score 7
- Selected patients with low-volume high-risk localised prostate cancer (T3a or Gleason score 8–10 or PSA >20ng/ml)
- Highly selected patients with very-high-risk localised prostate cancer (T3b–T4 N0 or any T N1) in the context of multimodality treatment

**RECOMMENDATIONS**

- Short-term (three months) or long-term (nine months) neoadjuvant therapy with gonadotrophin-releasing hormone analogues is not recommended in the treatment of stage T1–T2 disease
- Nerve-sparing surgery may be attempted in preoperatively potent patients with low risk for extracapsular disease (T1c, Gleason score ≤7 and PSA <10ng/ml)
- Unilateral nerve-sparing procedures are an option in stage T2a disease
Active surveillance
Active surveillance offers close monitoring of men with presumed low-risk prostate cancer. It has the benefit of avoiding any of the morbidity of radical treatments, but the disadvantage of potentially missing the window of opportunity for cure or effective treatment. It involves regular monitoring by a specialist prostate team using PSA, DRE, repeat biopsies (often now transperineal) and MRI imaging.

According to NICE, men with low-risk localised prostate cancer (see Table 1) who are considered suitable for radical treatment should first be offered active surveillance. Although there are many international and institutional criteria for active surveillance, it is particularly suitable for a subgroup of men with very low-risk, localised prostate cancer who have the following:
- clinical stage T1c/T2a
- Gleason score ≤6
- PSA <10ng/ml
- PSA density <0.15ng/ml per ml
- fewer than three out of 10–12 biopsy cores involved
- <10mm of any core involved
- are fit for radical treatment options, age 50–80 years.

The decision to change from active surveillance to radical treatment should be made in the light of the individual's personal preferences, comorbidities and life expectancy. Oncological reasons to stop active surveillance include increasing PSA, upgrading or increasing cancer volume at secondary biopsy.

Watchful waiting
Watchful waiting is the conservative management of prostate cancer, with PSA tests and symptom observation, until the development of local or systemic progression, at which point the patient would be treated for urinary tract symptoms or for palliation of metastatic lesions. It is particularly suitable for patients aged over 75 years or younger men with significant comorbidities.

The selection criteria for watchful waiting are:
- asymptomatic clinically localised prostate cancer
- clinical stage T1–3
- Gleason score ≤7
- any PSA level
- unsuitable for radical treatment (usually because of age or comorbidities).

HORMONAL THERAPIES
The goals of pharmacotherapy for prostate cancer are to induce remission, reduce morbidity and prevent complications. In localised prostate cancer, hormone therapy is given mainly as a neoadjuvant or adjuvant therapy with RP, EBRT or brachytherapy.

When given as a neoadjuvant agent, hormone therapy reduces prostate volume by 30–40 per cent, by reducing the tumour size, one can reduce the size of the treatment field and as a result the level of toxicity experienced. When compared with EBRT alone, a significant improvement in 10-year disease-specific mortality, distant metastases, disease-free survival and biochemical failure was seen with the addition of neoadjuvant hormone therapy, but no differences were observed in the risk of fatal cardiac events. The role of neoadjuvant hormone therapy with brachytherapy is controversial. It is used to reduce the prostate volume when it exceeds 50ml, to facilitate brachytherapy.

To date, evidence suggests that the downsizing achieved with neoadjuvant hormone therapy does not provide a survival advantage for patients with pathologically proven localised disease.

NOVEL THERAPIES
Novel therapies include high-intensity focused ultrasonography (HIFU) and cryotherapy.

High-intensity focused ultrasonography
Using ultrasound waves as a medium for energy transmission to heat tissue, HIFU causes coagulative necrosis of the prostate. It is used to treat low-volume intracapsular
prostate cancer. Certain centres offer targeted HIFU (focal therapy) to specific areas identified by biopsy within the gland. Organised results for this option are yet to be published, hence NICE classifies HIFU as an experimental therapy for use in clinical trials.

Cryotherapy

Cryotherapy is the application of sub-zero temperatures using liquid argon/nitrogen via hollow needles, which are inserted transperineally. It has historically caused severe side-effects such as rectovesical fistulas, incontinence and erectile dysfunction. It is usually recommended as a salvage treatment where brachytherapy or EBRT have failed. NICE also recommends cryotherapy only in the context of a clinical trial.

Guidelines on treatment options for localised prostate cancer are summarised in Table 2.

Declaration of interests: none declared.

REFERENCES


Table 2. Treatment options for men with localised prostate cancer

<table>
<thead>
<tr>
<th>Low risk</th>
<th>Intermediate risk</th>
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<td>Watchful waiting</td>
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<tr>
<td>Active surveillance</td>
<td>Preferred treatment</td>
<td>Treatment option</td>
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Radical treatments

| Prostatectomy | Treatment option | Preferred treatment | Preferred treatmenta |
| Brachytherapy | Treatment option | Treatment option | Not recommended |
| Conformal radiotherapyb | Treatment option | Preferred treatment | Preferred treatmenta |
| Cryotherapy | Not recommendedc | Not recommendedc | Not recommendedd |
| High-intensity focused ultrasound | Not recommendedc | Not recommendedc | Not recommendedd |

aOffer if there is a realistic prospect of long-term disease control.
bConformal radiotherapy should be given at a minimum dose of 74Gy (at a maximum of 2Gy per fraction).
cUnless as part of a clinical trial comparing use with established interventions.

dThe dose of radiation should be as low as possible, 45Gy.

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*Conformal radiotherapy should be given at a minimum dose of 74Gy (at a maximum of 2Gy per fraction).
*Unless as part of a clinical trial comparing use with established interventions.

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