The diagnosis and management of localised prostate cancer

Prostate cancer continues to be a major health issue. The treatment of patients with localised prostate cancer has developed over the last 15 years. Clinicians and patients need a clear understanding of the different treatment options available to allow for fully informed treatment decisions. In this article, we discuss the management of localised prostate cancer referring to the National Institute for Health and Clinical Excellence (NICE) guidance for the disease.

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In the last 10 years, prostate cancer has become the most commonly diagnosed malignancy among men in the UK, accounting for nearly a quarter of all new cancers in men (excluding non-melanoma skin cancer). In 2007, more than 36,000 new cases of prostate cancer were diagnosed in the UK and there were approximately 10,000 deaths related to the disease.[1]

With appropriate treatment, the majority of prostate cancers are potentially curable at presentation with five year survival rates approaching 77%.[2] For men with early localised disease, this figure can approach 99% at five years.[3] However, all treatments have the potential for side effects and these should be taken into consideration when reviewing potential treatment options.

A man's risk of developing prostate cancer is doubled if he has a first degree relative with the condition. If he has more than one first degree relative with prostate cancer, his risk of developing the disease himself increases by 5–11 fold.[4] There is a significant geographical and racial variation in prostate cancer incidence, with the highest incidence in Caribbean men, African-Americans in the USA (137 per 100,000 per year) and in Scandinavia, with the lowest incidence in Asia, particularly China (1·9 per 100,000 per annum).[5]

The Western diet, in particular high consumption of red meat, fat and dairy products, has been linked to prostate cancer, while diets high in phyto-oestrogens such as soya appear to have a protective effect.[6–7]

Diagnosis

Digital rectal examination (DRE), the level of serum prostate-specific antigen (PSA) and transrectal ultrasonography (TRUS) form the basis of establishing a diagnosis of prostate cancer. DRE allows local clinical staging and assessment of prostate size. Patients with abnormal DRE and persistently raised PSA with negative urinalysis are counselled towards having a prostate biopsy, with the benefits of early detection versus the risks of over treatment. Biopsy is associated with bleeding (60-80%), but this is rarely significant and usually settles within three to five days. Other risks include septicaemia, urinary retention and haematospermia. There is a 10-20% false negative biopsy rate.[8]

Most (>95%) primary prostate cancers are adenocarcinomas.[9] Each tumour has its own unique histopathological appearance, and the Gleason scoring system is used to describe these appearances. The two largest foci are given a grading score (1-5) and the two scores added to give a Gleason score (eg 4+3=7). The higher the score, the more aggressive the tumour pathologically, and, in general, this is associated with a poorer outcome. Modifications to the grading system have been made and low-grade tumours found in TRUS biopsies tend to be grouped as Gleason score 6.

Localised prostate cancer is confined to the prostate clinically and can be further divided into low-,

intermediate- or high-risk. These risk groups are based upon clinical stage, PSA prior to treatment, and Gleason grade at biopsy. The National Institute for Health and Clinical Excellence (NICE) recommends magnetic resonance imaging (MRI) for patients with suspected high-risk localised or locally advanced prostate cancer when radical treatment is intended.[10] A bone scan is not routinely advised for those patients with low-risk localised disease.

Management overview

NICE guidance[10] provides a patient-centred framework for managing localised prostate cancer. There are a wide number of treatment options available for men diagnosed with this type of prostate cancer. However, there is a paucity of randomised data comparing modalities, such as radical radiotherapy or radical prostatectomy. The UK ProtecT study[11] is investigating different treatment options (surgery, external beam radiotherapy, and active surveillance) for prostate cancer. It has yet to report, but may define the optimum treatment approach for early disease.

A multidisciplinary team approach is essential, with treatment being tailored to individual patient's requirements. Although each treatment may have potentially identical survival benefits, other important factors need to be considered (such as tumour characteristics, comorbidities, consideration of key treatment related toxicities and patient preference) when making a treatment decision.

The International Society of Geriatric Oncology (SIOG) has produced guidance for the management of older patients with prostate cancer.[12] It advises that treatment decisions are based on the patient's individual health status (eg, his comorbidities) rather than age. Other recommendations include offering curative treatment to older "fit" patients with prostate cancer and offering palliative care to those with terminal stage disease.

Active surveillance

Active surveillance involves monitoring a patient's cancer status with regular PSA measurements and repeated prostate biopsies. Radical treatment is initiated if progression occurs. Men with a Gleason score <3+4, with less than 50% biopsy cores involved, localised disease, and total PSA <15 ng/ml may be suitable candidates for active surveillance.[13,14] In one schedule, patients are followed with monthly PSAs during the first year and re-biopsy at 12 months, with indications for treatment being upgraded pathology on re-biopsy, change in PSA by >1 ng/ml per year, change in clinical stage or patient preference. This approach is different from the traditional method of infrequent PSA monitoring and no further biopsies in the patient managed by watchful waiting. As with radical treatment options for localised prostate cancer, an active surveillance approach requires a predicted 10-year life expectancy for the patient.

NICE recommends active surveillance as a treatment option for men with low and intermediate disease. However, the optimal protocol for the frequency of PSA testing and repeat biopsy is not known. Furthermore the rate of rise in an individual's PSA is an unreliable predictor of disease progression.[15] Despite this, large numbers of men do not need active treatment of their prostate cancer. Active surveillance series (ie, groups of patients from different institutions) report a prostate cancer mortality rate of 1-2% with eight year follow-up, and 20-30% of men receive radical treatment — either because of disease progression or patient preference.[16] Nevertheless, it remains only one of a number of choices for patients with localised disease and a full discussion of all treatment options is mandatory.

Traditional watchful waiting is considered as an option for men with low-grade, low-volume prostate cancer whose age or comorbidities mean that they are more likely to die of other causes rather than their prostate cancer. For these patients, a three to six monthly follow-up schedule is recommended with treatment implemented when symptoms intervene, and many patients can safely be managed in the primary care setting.

Radical prostatectomy

Radical prostatectomy involves the removal of the entire prostate, seminal vesicles, and frequently the obturator lymph nodes, allowing complete surgical staging. It may be performed via the retropubic approach, either through a small (6–10 cm) incision or using a laparoscopic or robotic technique. Less commonly, a perineal approach may be used.

Laparoscopic prostatectomy, which may be robot-assisted, is increasingly popular due to reductions in post-operative stay, potential reductions in blood loss and improved visualisation of the surgical anastomosis

being linked to early and better continence rates. Significant cost and limited availability currently restrict robotic radical prostatectomy to selected UK centres. There are no randomised trials comparing cancer-specific outcomes of open, laparoscopic and robotic prostatectomy. However, data from single institution series appears to be comparable, albeit with limited long-term follow-up.[17]

There is level one evidence[18] to show that surgical treatment improves absolute survival in localised disease when compared with watchful waiting. It should be borne in mind that much of the evidence for watchful waiting included patents who would not be considered suitable for active surveillance (eg serum PSA >20, clinically palpable disease), and who were not managed with the intensive follow-up schedule mandated as part of active surveillance. At 10 years, there was a significant difference in disease free survival (DFS) of 44% and in overall survival (OS) of 26% in favour of radical prostatectomy. The absolute risk reductions, however, were modest (5% DFS, 5% OS). This translates to needing to treat 20 men with radical prostatectomy for one man to benefit by 10 years. The use of adjuvant and neoadjuvant hormone therapy with radical prostatectomy have been suggested but no level one evidence supports its clinical benefit in terms of DFS. Therefore, it is not recommended outside the context of clinical trials.

After radical prostatectomy, serum PSA should fall to an undetectable level within a month of surgery. Regular follow-up including PSA checks can detect recurrent disease eight years before metastases develop. If metastases do develop, follow-up can detect recurrent disease a further five years before death from prostate cancer.[19] In the event of a PSA rise, further treatments can be offered with potentially curative intent dependent on the original stage of tumour, presence of positive margins at time of surgery, and rate of PSA rise. This includes external beam radiotherapy to the prostate bed if local recurrence is suspected or palliative treatment with hormonal manipulation if systemic disease is suspected.

The reported incidence[20] of post prostatectomy incontinence (PPI) ranges widely from 8% to 77% depending on how incontinence is defined, the timing since the operation, and the available investigations. The MAPS study[21] suggests that in the UK, nearly 40% of men following radical prostatectomy remain significantly bothered by their incontinence at 12 months post surgery. Post-operative pelvic floor exercises and new, minimally invasive techniques have helped to improve the return to continence. Patients with troublesome symptoms will need review by a specialist continence service as treatments vary from conservative approaches through to artificial urinary sphincters in a small number of patients.

External beam radiotherapy (EBRT)

EBRT uses high-energy photon beams focused on the prostate to damage tumour DNA. In the last two to three decades, advances in radiation techniques (including 3D-conformal RT and the introduction of CT-based treatment planning) have led to substantial improvement in targeting the prostate and delivering higher doses of radiation. As a result, there has been a significant reduction in toxicity to the surrounding structures, including bladder, bowel, femoral heads and rectum.

Conformal radiotherapy allows shaping of the beam to "conform" directly to the shape of the prostate in three dimensions. This significantly reduces the risk of radiation proctitis, the dose-limiting side effect of prostate EBRT.[22] NICE recommends conformal radiotherapy as the standard modality of radiotherapy.[23] In general, one out-patient treatment is required to plan radiotherapy using a dedicated planning CT, and treatment is usually given daily on successive weekdays over 4-7·5 weeks. Dose escalation has shown improvements in biochemical outcome,[24] and the dose equivalent of 74 Gray is the approved standard of care in the NICE guidance for prostate cancer.[10]

Image guided radiotherapy (IGRT) is a significant development in verifying the position of the prostate prior to treatment delivery, using cross sectional imaging. During treatment, any alteration in rectal size can displace the prostate from its original position on the radiotherapy planning CT scan. This can lead to both a geographical miss of the tumour and over treatment of normal tissue. Historically, verification of position has been made using bony landmarks. The advent of IGRT allows more precise verification by matching to soft tissue or to implanted markers into the prostate, such as gold seeds, thereby improving accuracy of treatment.

Standard radiotherapy treatment for intermediate- and high-risk disease includes a period of three months of luteinising hormone releasing hormone (LHRH) agonist prior to radiotherapy. The initial stimulation of the pituitary by these agonists can cause a surge in testosterone, hence the need for anti-androgen cover

prior to the first LHRH injection. A three-month course of neoadjuvant LHRH treatment leads to a reduction in prostate size (cytoreduction) of 20-50%,[25] enabling smaller volumes to be treated and reducing the amount of irradiated normal tissue. There is also increased radiosensitivity.

Emerging data for degarelix,[26] a novel LHRH antagonist are available. The mechanism of this agent allows more rapid achievement of castrate levels of serum testosterone, which may confer a clinical advantage when compared with traditional LHRH analogues and also reduce the need for cover of tumour flare after first injection. A current commercially sponsored study comparing reduction in prostate volume prior to radical prostate radiotherapy after three months of either goserelin (an LHRH analogue) or degarelix is currently recruiting worldwide.[27]

Acute side effects as a result of "normal tissue" exposure usually start midway through the treatment course and peak 10 days after completing radiotherapy. They include diarrhoea (managed with a low-fibre diet and loperamide), tenesmus and proctitis, for which proctosedyl suppositories may be of benefit. A high-fluid intake is recommended to reduce dysuria and frequency. Lethargy is common. Acute effects usually resolve within six weeks of completing treatment.

Side effects occurring more than three months after the end of radiotherapy are termed "late side effects" and may include impotence in 10-30% of men.[28] This may be confounded by the use of neoadjuvant or adjuvant hormonal therapy. Incontinence is very unusual and mild disturbance in stool frequency and consistency occurs in less than 20% of men. A small minority of men develop chronic proctitis, giving rise to bleeding and fibrosis, with a <1% risk of surgical intervention.[29] Bowel complications persisting for more than six months require further investigation to exclude any underlying bowel neoplasm. Rectal or bladder tumours cancers may occur as a result of pelvic irradiation and are seen in <1% of men 15 years after prostate radiotherapy.[30] NICE recommends that men are offered flexible sigmoidoscopy every five years after prostate radiotherapy.

Brachytherapy

Prostate brachytherapy involves the direct insertion of radioactive sources into the prostate, allowing a high dose of radiation to be given over a short distance around the source, thus sparing normal tissue. Two types are used in the treatment of localised prostate cancer, iodine–125 or palladium–108 seeds as a permanent low-dose implant, and iridium–192 as a temporary, high-dose implant used in conjunction with EBRT. The selection criteria are different for both types of treatment, and brachytherapy is available only in specialist centres.

Eligible patients for low-dose rate brachytherapy are those who meet the following criteria: life expectancy >10 years, clinically localised cancer of Gleason 7 or less, prostate volume </=50 cc, and no previous transurethral resection of the prostate (TURP). A TRUS is performed to assess prostate volume and plan treatment. Using the TRUS as guidance, 20–30 hollow needles are subsequently placed percutaneously in the prostate using a perineal template. Up to 120 seeds are implanted, conforming to the prostate shape and sparing the area close to the urethra. The procedure is carried out using spinal or general anaesthesia and usually requires an overnight stay.

Some centres use a temporary high-dose rate brachytherapy implant as a boost after EBRT for patients with high-risk disease. Hollow rods are placed in the prostate using the TRUS as guidance. The patient often receives three separate doses with a minimum of six hours between each dose. The rods remain in-situ throughout the treatment so the patient is kept in the lithotomy position for at least 18 hours and backache is a common problem.

The side effects of brachytherapy are incontinence and erectile dysfunction, similar to EBRT, with the added complication associated with the anaesthetic. There is also a risk of urethral stricture in 6% of men.[18] Despite this, excellent PSA free rates of 79-89% at five years have been reported in men with high-risk disease.

Novel therapies

Cryotherapy and High-Intensity Focused Ultrasound (HIFU) are two minimally invasive modalities in the primary and salvage treatment of localised prostate cancer. However, they are not currently recommended by NICE outside of clinical trials, due to the relatively limited published data and the lack of long-term follow-up evidence.

Prostate cryotherapy is the ablation of the prostatic tissue by thermal therapy at extremely low temperatures (-20 to -40 °C) under ultrasound guidance. It results in destruction of the gland by central coagulation necrosis surrounded by a peripheral layer of apparent apoptosis.

PSA nadir is usually achieved within three months. Erectile dysfunction, urethral injury and recto-urethral fistulae are recognised complications.

HIFU uses selective destruction of the targeted prostatic tissue by using high-energy ultrasound waves generating high temperatures (up to 85°C) resulting in necrosis 3-5 cm away from the transrectal probe without injuring the intervening tissue.

Both HIFU and cryotherapy remain experimental in both first-line and salvage settings for localised prostate cancer. Patients should be counselled with regard to this before undergoing treatment. While they may represent an attractive option for patients with low-risk disease, who desire a radical treatment with potentially fewer side effects than those seen with the gold-standard modalities of surgery and radiotherapy, better long-term outcome and toxicity data is required.

Androgen suppression therapy

As discussed earlier, hormonal therapy can be used in the neoadjuvant setting prior to radical radiotherapy or as adjuvant therapy after definitive EBRT. It can also be used in the palliative setting for patients with intermediate or high-risk localised disease who have a life expectancy of less than 10 years, significant comorbidities or who do not accept definitive local treatment. Androgen ablation may be achieved by surgical or chemical castration with LHRH analogues or with the use of anti-androgen monotherapy

LHRH produced by the hypothalamus stimulates the anterior pituitary gland to release LH, which in turn results in the production of testosterone. Administration of LHRHa causes stimulation of pituitary LHRH receptors leading to an initial testosterone surge followed by down-regulation of LH production and subsequent castrate levels of androgens. The initial surge of testosterone may lead to the tumour flare phenomenon and should be prevented by a short course of an anti-androgen taken two weeks prior and subsequent to the first dose of LHRHa.

LHRHa (including goserelin and leuprorelin) can be given subcutaneously or intramuscularly as depot injections either on a monthly or three monthly basis. The average response duration is two years.

Anti-androgens cause blockade of testosterone receptors on tumour cells and can be used to achieve maximum androgen blockade in patients who continue to produce levels of serum testosterone greater than 0·5 ng/ml or who have developed castrate resistant disease on an LHRH analogue. They may be used as monotherapy in patients with locally advanced disease and as an alternative to LHRH analogues for patients receiving adjuvant hormonal therapy after definitive radical radiotherapy for locally advanced disease. Bicalutamide appears to have tumour responses equivalent to LHRH analogues with potentially better preservation of bone mineral density, overall vitality and potency, albeit at the expense of increased gynaecomastia and breast tenderness.[31]

Conclusion

Localised prostate cancer presents a challenge to the clinician: the natural history is variable and the biological behaviour varies significantly between patients. For many patients, they are more likely to live with their tumour rather than die because of it. As clinicians, we need to provide patients with the information and support to allow them to make the choice of treatment that is right for them. There is an urgent need for more sensitive clinically relevant markers of prostate cancer progression. This will allow men with potentially lethal disease to undergo the optimum cancer curing treatment, while safely deferring treatment in those with less aggressive biologically indolent disease.

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