Prostate cancer: part two – clinical management

Prostate cancer has overtaken lung cancer to become the most commonly occurring cancer in men in the Western world. In part one (*GM October, 2006*) of this two-part series, **Drs Nishi Gupta, Heather Payne, Omar Al Salihi** and **David Gillatt** discussed the structure of a multidisciplinary approach and some of the new management tools available to provide the best treatment for patients. They conclude the series by discussing best clinical management.

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There are now over 30,000 new cases of prostate cancer diagnosed per year in the UK and it accounts for one in five of all new male cancers[1]. It is largely a malignancy of the older population with incidence rates rising sharply with age; for men aged 65–69 the incidence rate per 100,000 men is 449, by age 75–79 it is 757 and the rate increases to 970 by 85 or more years[1].

Though the incidence of prostate cancer has risen in the last 20 years, the mortality has remained relatively stable. An increasing use of prostate-specific antigen (PSA) screening and advances in diagnostic techniques have led to prostate cancer being diagnosed at progressively earlier stages, resulting in a lower risk of death in the majority of cases. However, the mortality rate for prostate cancer stands at 10,000 men per year in the UK[2] and is the second most common cause of cancer-related death for men, accounting for 14 per cent. The challenge is to identify and treat patients most at risk of dying from prostate cancer, as opposed to those who have less aggressive disease and will die with their prostate cancer – not from it.

Diagnostic tests and staging

The investigations for the diagnosis and staging of prostate cancer are:

> digital rectal examination (DRE) to determine local involvement of the disease, including any extracapsular spread or seminal vesicle involvement;

> PSA, which is influenced by age, prostatitis, acute urinary retention and benign prostatic hypertrophy;

> transrectal ultrasound (TRUS) with needle biopsy, preferably to obtain six to eight[4] systematic core biopsies as a representative sample of the prostate gland, which should be histologically analysed using the Gleason Grading System (*Table 1*).

Table 1. Gleason grade scoring[3]

Prostate cancer biopsy is analysed according to:

> degree of glandular differentiation

> relationship of glands to stroma

> graded one to five (one = well differentiated; five = poorly differentiated

> the two most commonly occurring grades summed up to give total Gleason score (minimum two; maximum 10).

Prostate cancer can be further staged with a bone scan and CT/MRI scan of the pelvis in order to determine any evidence of nodal or distant metastases. The most widely used staging system

for prostate cancer is the TNM (tumour, nodes and metastasis) definition devised by the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer[5] revised in 2002 (*Table 2*). Prostate cancer can be divided into three groups:

- localised (confined to prostate, ie, T1/T2 N0);
- locally advanced (extracapsular spread or nodal disease, ie, T1/T2/N+ or T3/T4N0/N+);
- advanced (metastatic, ie, any T/N M1) .

Localised cancer can be further stratified into three risk groups (low, intermediate and high risk) according to the three main criteria at diagnosis: Gleason grade, pre-treatment PSA and TNM stage. These three parameters are established prognostic factors used to predict the risk of microscopic metastases and of PSA relapse after treatment[6].

Multidisciplinary meeting (MDM)

Once a diagnosis of prostate cancer has been made and the relevant staging investigations performed, the case should be discussed within a MDM consisting of a urological surgeon, clinical and medical oncologist, radiologist, histopathologist and specialist nurses to provide an integrated care approach for each patient. The function of the MDM is to recommend treatment options for patients after considering prostate cancer factors such as extent of disease, overall prognosis, patient factors (including co-morbidity, type and severity of symptoms, sexual function and lifestyle) and treatment side effects – in particular, impotence. It is fundamental that patient preference should be discussed by the MDM to ensure he can participate fully in the treatment decision. The MDM can highlight any patient suitable for participation in ongoing clinical trials, facilitate audit and initiate further research projects.

Treatment options

Localised disease

There are a variety of treatments available for men with localised prostate cancer who are usually asymptomatic from their cancer and diagnosed as a result of routine PSA testing or as part of ongoing investigations for other co-morbid conditions.

Active surveillance is a relatively novel approach to the management of early prostate cancer. It aims to reduce the side effects of therapy without compromising survival. Men are monitored regularly with PSA tests, prostate imaging and

Table 2. TNM definition of prostate cancer[5]

Primary Tumour (T)

TX: Primary tumour cannot be assessed

T0: No evidence of primary tumour

T1: Clinically inapparent tumour not palpable nor visible by imaging:
T1: Clinically inapparent tumour not palpable nor visible by imaging
T1a: Tumour incidental histological finding in ≤five per cent of tissue resected
T1b: Tumour incidental histological finding in >five per cent of tissue resected
T1c: Tumour identified by needle biopsy (eg, because of elevated PSA)

T2: Tumour confined within prostate
T2a: Tumour involves 50 per cent of ≤1 lobe or less
T2b: Tumour involves >50 per cent of one lobe but not both
T2c: Tumour involves both lobes

T3: Tumour extends through the prostate capsule
T3a: Extracapsular extension (unilateral)
T3b: Extracapsular extension (bilateral)
T3c: Tumour invades seminal vesicle(s)

T4: Tumour is fixed or invades adjacent structures other than seminal vesicles
T4a: Tumour invades external sphincter and/or bladder neck and/or rectum
T4b: Tumour invades levator muscles and/or is fixed to pelvic side wall

Regional lymph nodes (N)

NX: Regional lymph nodes were not assessed

N0: No regional lymph node metastasis

N1: Metastasis in single regional lymph node, two cm or less in greatest dimension

N2: Metastasis in single lymph node more than two cm but not more than five cm in greatest dimension or multiple lymph nodes, none more than five cm in greatest dimension

N3: Metastases in lymph node(s) more than five cm in greatest dimension

Distant metastasis (M)

MX: Distant metastasis cannot be assessed (not evaluated by any modality)

M0: No distant metastasis

M1: Distant metastasis
M1a: Non regional lymph nodes
M1b: Bone metastasis
M1c: Metastasis in other sites

often repeat biopsies. They undergo radical treatment with curative intent if the disease becomes more biologically aggressive as demonstrated by PSA kinetics or repeat biopsy findings. Patients suitable for active surveillance are those with low-risk localised disease who are fit for radical treatment. Ongoing prospective studies of active surveillance[7] have shown that 60–80 per cent of such men will avoid the need for treatment. Active surveillance should be distinguished from watchful waiting. Traditional watchful waiting involves relatively lax observation with late, palliative treatment for those who develop symptoms of progressive disease. In contrast, active surveillance involves close monitoring with early radical treatment.

Watchful waiting is a strategy to delay or avoid treatment and, consequently, any side effects. Patients are observed and treated when they have symptoms. In contrast to active surveillance, PSA testing is not so rigorous with a watchful waiting policy and the aims are to achieve symptomatic control. Albertson[8] recently estimated a 20-year survival for men with clinically localised prostate cancer based on a competing risk analysis for causes of death. The results showed men with low grade tumours have only a small risk of dying from their prostate cancer during 20 years of follow-up (Gleason score two to four, six deaths per 1,000 person-years). This contrasts with high grade tumours when there is a high probability of dying from prostate cancer within 10 years of diagnosis (Gleason score of eight to 10, 121 deaths per 1,000 person-years).

Radical therapy: prostatectomy and radiotherapy (external beam or brachytherapy) are used to treat prostate cancer radically. There has been no randomised study directly comparing these treatments but efficacy is thought to be equivalent for localised disease. ProtecT is a UK randomised controlled trial currently recruiting patients and designed to compare surgery, radiotherapy and active monitoring in early prostate cancer. This may help to clarify this issue. These treatments all have differing profiles and related toxicity – and this will often drive the patients' decision.

Radical prostatectomy (RP) can be achieved with a number of different techniques. Radical retropubic prostatectomy (RRP) is the most commonly performed operation in the UK but some urologists use a perineal approach. In 2002, the National Institute for Health and Clinical Excellence (NICE) reviewed a total of 17 studies in order to investigate the efficacy of radical prostatectomy for men with localised prostate cancer. Cancer-specific survival after 10 years of follow-up ranged from 86–91 per cent, with clinical disease-free survival ranging from 57–83 per cent. A randomised study of RP *vs* watchful waiting has been reported by Bill-Axelson *et al*[9]. The results demonstrated only a small absolute reduction in the risk of death after 10 years, but the reductions in the risks of metastasis and local tumour progression were substantial. This has to be balanced against the side effects of RP, which include urinary dysfunction and impotence. The risks of erectile dysfunction vary with technique and extent of tumour, and are commoner in men over the age of 65. Generally, potency can be retained in 68 per cent of patients with bilateral nerve-sparing prostatectomy and in 13–47 per cent of men with unilateral neurovascular bundle preservation. Overall, around 80 per cent of men report erectile problems[10]. Significant urinary incontinence (total) is less than five per cent. Laparoscopic prostatectomy is becoming increasingly available according to local expertise and has the advantage of a shorter hospital admission and convalescence though the incidence of side effects is similar to that seen after RRP.

External beam radiotherapy (EBRT) or 'conformal' radiotherapy (ie, shaping the beam to the prostate gland in three dimensions) is widely available in radiotherapy departments today and has permitted higher dose delivery to the prostate while sparing normal tissues. Studies have shown that dose escalation to ≥70Gy results in better disease control[11] with acceptable side effects. The delivery of these higher doses were not previously possible using conventional, two dimensional radiotherapy planning[12]. In 2002, NICE also reviewed radiotherapy studies and found survival and recurrence rates associated with grade and stage of the disease. The five-year survival for those with T1–T2 stage disease averaged 70–80 per cent. Local progression was observed in 10–20 per cent of these patients. However, improved selection and technical developments in radiotherapy leading to increased doses are showing better results. Acute toxicity of radiotherapy includes diarrhoea, cystitis and tiredness, and long-term morbidity includes impotence (50 per cent) and proctitis (<five per cent). Patients with significant bowel disease or bilateral hip replacements are unsuitable for radiotherapy.

Table 3. Profile of gonadotrophin releasing hormone (LHRH) agonists

- LHRH agonists suppress testosterone production by the testes through positive feedback of GnRH at pituitary level.
- LHRH analogues include goserelin and leuprorelin acetate.
- Administered by subcutaneous injection, monthly or three-monthly.
- Associated with initial tumour flare prevented by anti-androgen given two weeks before and two weeks after first injection.
- Side effects include impotence, loss of libido, osteopenia/osteoporosis, hot flushes, gynaecomastia and weight gain.

Neo-adjuvant hormones usually in the form of a lutenising hormone-releasing hormone (LHRH) agonist (*Table 3*) can be given for three months before commencing radiotherapy and can cause a 25–30 per cent reduction in the size of the prostate and potentially allow smaller fields of radiotherapy to be used with sparing of the rectum and bladder. High risk localised tumours are usually treated with long-term adjuvant hormone therapy as will be described in the section on locally advanced prostate cancer.

Low dose rate (LDR) brachytherapy is a minimally invasive procedure involving the insertion of radioactive seeds (I 125) into the prostate gland, thereby irradiating the prostate directly while minimising toxicity to surrounding normal structures. The seeds are permanently implanted into the prostate via needles using a percutaneous transperineal approach under general anaesthetic. This treatment is restricted to men with a small prostate (< 50cc), who have not had a previous transurethral resection of the prostate (TURP) or significant urinary obstruction. Initial urinary discomfort is approximately 50 per cent but long term complications, such as incontinence and diarrhoea, are minimal and impotence rates are reduced to six to 30 per cent.

Locally advanced (non-metastatic) disease

This group of patients includes those with locally advanced or node positive prostate cancer and management options are often the same for those

men with high risk localised (poor prognostic features such as PSA ≥20 and/or Gleason Grade ≥eight).

Hormone therapy is often the mainstay of treatment for locally advanced prostate cancer as there is a high risk of microscopic metastases. It can be used alone or in combination with radiotherapy. There appear to be advantages of starting hormone therapy early rather waiting until symptoms progress[13]. LHRH agonists are often used to treat locally advanced prostate cancer. Data from the Early Prostate Cancer (EPC) Programme have shown use of the non-steroidal anti-androgen, bicalutamide, compared with watchful waiting, significantly increases disease progression-free survival[14]. Bicalutamide has some advantages over castration-based therapy in that it can maintain physical capacity and bone mineral density and reduces the risk of hot flushes and loss of sexual function, but can cause gynaecomastia and mastalgia.

External beam radiotherapy and hormones is rapidly becoming accepted as standard practice. The benefits of dose escalation are greatest for high risk prostate cancers, but there is no consensus as to the optimal way of delivering these high doses of radiation. Methods include 3D conformal radiotherapy, intensity modulated radiotherapy and the use of a high dose rate brachytherapy boost. The treatment fields include the prostate gland and seminal vesicles. There is controversy regarding irradiation of the pelvic lymph nodes; advocates propose an advantage in local control, while others believe it simply increases toxicity. EBRT alone has been shown to have a poorer outcome than in localised prostate cancer making this combination therapy with radiotherapy and hormonal treatment the more effective choice.

Neo-adjuvant hormones are used to reduce tumour bulk prior to radiation therapy and this combination was used in the RTOG 86-10 study[15]. This demonstrated a significant improvement in disease-free survival for locally advanced prostate cancers and an increase in overall survival for the sub group with Gleason Grade two to six. Adjuvant androgen suppression immediately after radical radiotherapy has been shown to significantly increase overall survival, progression-free survival and significantly reduce local progression, distant metastases and biochemical progression in several large randomised studies using goserelin[16,17]. There is still some debate regarding the optimal timing

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Key points

- Prostate cancer is a common malignancy but one which can range from slow growing to highly aggressive.
- Prostate cancer is divided into localised, locally advanced (non-metastatic) and advanced (metastatic) stages (depending on the extent of the primary disease, and the presence of nodal and/or metastatic spread) at diagnosis.
- Localised prostate cancer has several treatment options available, depending on other risk factors (Gleason Grade and PSA).
- Treatment strategies should always be discussed in a MDM and therapy tailored according to patient characteristics and preference.

and duration of hormone treatment, but it is usually between two to three years. The EPC study has also recently demonstrated a significant increase in overall survival with the addition of bicalutamide to radical radiotherapy in men with locally advanced disease. It can be used as an alternative to LHRH agonists in this setting[18].

Advanced (metastatic) disease

The number of patients presenting with metastatic prostate cancer has fallen to under 15 per cent in Europe. The main site of metastasis is via haematogenous spread to the bones, most commonly the lumbosacral spine and the axial skeleton. The principle treatment in the absence of an oncological emergency (eg, cord compression) is with androgen deprivation achieved by either orchidectomy or hormonal therapy with LHRH agonists. These two methods achieve similar rates and duration of response[19], although surgical castration is infrequently performed now. In addition, adequate analgesia, local treatment with radiotherapy, bisphosphonates and active support from the palliative care team are all essential components of management.

Hormone therapy and early use of LHRH agonists is recommended in patients presenting with metastatic prostate cancer. Response rates of over 85 per cent are expected for up to three years[20]. Intermittent androgen deprivation (IAD) is being studied in clinical trials in an attempt to improve quality of life and delay the hormone resistance that typically results in treatment failure. IAD involves the cessation of LHRH agonists once an adequate PSA reduction has been achieved with re-introduction of treatment as PSA begins to rise. The concurrent use of anti-androgens (maximum androgen blockade or MAB) with LHRH agonists can be used as second-line treatment in patients who have disease progression on LHRH agonists alone. Second-line hormone therapy with MAB can produce response rates of up to 30–50 per cent with an average duration of six months or more. Withdrawal of the anti-androgen for PSA relapse while on MAB can also result in further responses of 20–30 per cent, with an overall duration of four to five months. Other hormonal manipulation may be attempted as third- and fourth-line therapies. Diethylstilboestrol and or hydrocortisone can sometimes achieve further remissions of up to six months or more. Oestrogen therapy is associated with gynaecomastia, fluid retention and thromboembolism. Cardiovascular events can be prevented with aspirin or anticoagulants.

Hormone resistant prostate cancer (HRPC) leaves limited treatment options. Until recently, when the disease became hormone refractory the standard of care has been mitoxantrone chemotherapy combined with prednisolone. This therapy improves bone pain in 30 per cent of men, but has not been associated with increased survival. Two recent studies with docetaxol have demonstrated better symptomatic relief compared with mitoxantrone and prednisolone and also significantly prolonged survival[21,22]. The optimal sequencing of chemotherapy remains uncertain and is again the subject of ongoing clinical trials. There are other new agents showing promise in HRPC, and this remains a challenging therapeutic area.

Summary

Prostate cancer is a common malignancy that encompasses a spectrum of disease ranging from relatively indolent to highly aggressive. The older population is most commonly affected and appropriate management must be selected to balance the potential mortality of the cancer *vs* the morbidity of treatment. The MDM provides a suitable forum where all these factors can be discussed and has been shown to improve disease management, patient experience and health worker satisfaction

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