UROLOGICAL MALIGNANCY—1: PROSTATE CANCER

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Symptoms and signs

Haemospermia

- Patients with haemospermia often present to their general practitioner thinking that they may have cancer
- Haemospermia is usually related to non-specific inflammation of the prostate and settles spontaneously

The symptoms and signs of prostate cancer are initially closely similar to those of benign prostatic hyperplasia—obstruction of the urethra by the malignant gland may lead to hesitancy, poor urinary flow, intermittent flow, post-micturition dribbling, and incomplete emptying. Secondary bladder instability may ensue and give rise to urinary frequency, nocturia, and urgency.

Onset

- Prostate cancer typically proceeds insidiously
- Men often present late with advanced disease and symptoms resulting from bony metastasis or from anaemia of chronic disease

The patient may also present with haematuria, typically reporting that the blood appears at the beginning of an otherwise clear urinary stream. Although this suggests a cause localised to the lower urinary tract, all such patients should be investigated and managed along the lines described for patients with haematuria (see next article in the series).

Investigations of patients with suspected prostate cancer

Normal ranges for prostate specific antigen

Polyclonal assay	0-2.5 ng/ml
Monoclonal assay	0-4 ng/ml

Investigations begin in the same way as for patients with benign prostatic hyperplasia—a full history of the main symptoms, followed by a thorough clinical examination and digital rectal examination. There are few clinical signs in early prostate cancer, but digital rectal examination will often detect an early lesion. In prostate cancer either the normal smooth surface of the prostate may be replaced by a hard nodule or the gland itself may be enlarged, hard, and “craggy” to the touch. The normal midline sulcus may be lost.

The serum prostate specific antigen level should be established. Normal ranges depend on the assay used.

Technique of transperineal prostate biopsy. The operator guides the needle into the prostate with finger placed in rectum.

Transrectal ultrasound scan showing prostate cancer (arrow) bulging anteriorly through prostate capsule.

Whether to proceed with a transrectal ultrasound examination and biopsy has been the subject of much debate, but current recommendations suggest that most men with either an abnormal finding on digital rectal examination or a raised prostate specific antigen value should have a transrectal biopsy with ultrasound guidance. This recommendation should be considered in the context of the individual patient, and elderly or frail men with no other signs of cancer may be successfully managed by close observation. Biopsy is not without complications (particularly infection and bleeding), and this should be remembered when considering a biopsy. The rise in prostate specific antigen over time can also be used to discriminate between benign prostatic hyperplasia and prostate cancer, and a value rising by more than 0.75 ng/ml a year has been suggested as the cut off point for these two conditions.

Screening for prostate cancer

Screening

- The value of screening for prostate cancer has been much debated by urologists
- Proponents cite as justification the fact that the incidence of prostate cancer is rising by 3% a year
- Prostate cancer is now the second commonest cause of death from cancer in men in northern Europe

Several problems have beset the widespread acceptance of screening. Firstly, the correct protocol has yet to be established. Digital rectal examination as a screening tool relies heavily on the experience of the examiner. If digital rectal examination alone is used, one third of patients diagnosed with prostate cancer will have incurable disease. Transrectal ultrasonography, when used alone, has low positive and negative predictive values and so is not recommended as a screening tool—it should be reserved for guiding the urologist's needle during biopsies. Determining the prostate specific antigen level remains the most useful tool for screening, and several recent studies have confirmed its specificity.

Differences between cancers detectable with prostate specific antigen value and clinically unimportant cancers not detectable till postmortem examination

- Cancers that are detectable by use of prostate specific antigen values may be more likely to be clinically relevant
- Cancers detected by use of prostate specific antigen values are frequently either poorly differentiated or spread widely throughout the prostate
- Most cancers detected by use of prostate specific antigen values will be reclassified to a higher clinical stage when removed at radical prostatectomy

Secondly, one of the concerns about routine screening for prostate cancer is that either (a) it may detect patients who have prostate cancer that has spread beyond the prostate capsule (and is thus incurable) or (b) small tumours that will be clinically unimportant during the lifetime of the patient may be discovered, the treatment of which may cause appreciable morbidity. At postmortem examination about one third of men aged over 75 years will have clinically unimportant microscopic foci of cancer in the prostate that cannot be detected by current methods. However, cancers detectable by determination of prostatic specific antigen level may differ from these unimportant cancers.

Thus screening with use of prostatic specific antigen values seems to have the potential to detect clinically important disease.

Management of prostate cancer

Diagrams showing first two stages of prostate cancer: T1—clinically inapparent cancer; T2—palpable disease confined to prostate.

Localised disease

Patients in this group comprise those with clinically inapparent disease (stage T1 in the tumour, node, metastases (TNM) classification system) and those with palpable disease confined to the prostate (stage T2).

Many men are discovered to have prostate cancer after histopathological examination of prostate chips removed during a transurethral prostatectomy for bladder outflow obstruction, presumed to be due to benign prostatic hyperplasia.

Patients with a life expectancy of less than 10 years and stage T1a disease are probably best managed by regular follow up, as few such cancers will progress over the next 10 years. Higher stage disease in these patients (but still localised to the prostate) should be managed by radiotherapy or hormonal therapy. Patients whose life expectancy is more than 10 years should be given the choice of either radical prostatectomy or radiotherapy, although stage T1a disease can initially be managed by surveillance.

Radical prostatectomy is associated with an impotence rate of 30–60%, although impotence is less common when nerve sparing approaches are used. Urinary incontinence (incidence of 5–15%) may respond to drugs, although implantation of an artificial urinary sphincter may be needed.

Radiotherapy in localised disease (stage T1 or T2) is the preferred treatment for older patients and those whose health status or grade of tumour precludes curative surgery. Impotence is a side effect in up to 60% of patients, but 15 year disease-free survival rates of up to 85% have been achieved.

Diagrams showing third and fourth stages of prostate cancer: T3—locally advanced disease, with tumour extending beyond prostate capsule; T4—disseminated disease, showing metastasis to femur.

Locally advanced disease

In patients with locally advanced disease (stage T3) the emphasis is not to cure as most men will have occult metastatic disease. The preferred treatment for these patients is radiotherapy, although radical prostatectomy is sometimes performed as a salvage procedure when radiotherapy fails.

Disseminated disease

Most patients with disseminated disease (stage T4) are treated with hormonal therapy, although the correct time to start such treatment remains unclear. Symptomatic men should begin treatment immediately, whereas those without symptoms may be spared treatment until symptoms develop.

Hormonal therapies are based on the suppression of testosterone production or competition with its effects. Cyproterone acetate is an antiandrogen which acts by preventing the active metabolite of testosterone—dihydrotestosterone—from binding to intracytoplasmic protein complexes within the prostate cell and thus reduces prostatic cell growth. Luteinising hormone-releasing hormone agonists, such as goserelin, act by initially stimulating the release of gonadotrophins by the pituitary, before causing an inhibition. For this reason an antiandrogen should be given before the use of a luteinising hormone-releasing hormone agonist to prevent the transient stimulation of tumour growth. On occasions such tumour stimulation may lead to compression of the spinal cord by bone metastases or to urinary retention.

Bilateral subcapsular orchidectomy is as effective as either of the above treatments and removes the need for continued therapy. However, many men find the thought of surgical castration unpalatable.

Recent advances

Recent advances in management of prostate cancer

Intracrinology

- Intracrinology is the study of the synthesis of active steroids in peripheral target tissues
- It has recently been shown that the adrenal may be the source of inactive steroid precursors, which are converted into active metabolites in the prostate
- Studies have shown that medical or surgical castration remove serum testosterone, but dihydrotestosterone levels in the prostate are less affected, showing the importance of adrenal androgens
- The combination of medical castration and inhibition of action of dihydrotestosterone together (maximal androgen blockade) has been shown to produce a small improvement in response rates in some patients with prostate cancer

Apoptosis

- Apoptosis describes a complex mechanism of programmed cell death by which effete cells are removed from a tissue
- The regulatory pathways of apoptosis may be switched off in malignant tissues
- Removal of androgens by medical or surgical castration induces androgen dependent prostate cancer cells to undergo apoptosis, but most patients relapse when androgen independent cells become the dominant cell type
- Radiation and certain cytotoxic drugs may achieve their beneficial effects by inducing apoptosis in this androgen independent cell population

Key references

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The source of the ultrasound scan was Dr M J Kellett, Middlesex Hospital, London.

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