Prostate cancer: management and controversies

Frank Lee, Hitendra RH Patel

Advances in the management of prostate cancer are associated with uncertainties and controversies in screening, who and when to treat, the best treatment option for localized disease and what to do with biochemical relapse after presumed curative treatment.

Prostate cancer is now the most common cancer diagnosed and the second most common cause of cancer death in men. Improvements in detection include prostate specific antigen (PSA) testing and transrectal ultrasound guided biopsy of the prostate. They allow the detection of the disease at an early stage when it is organ-confined and amenable to curative treatment. Refinements in surgical and radiotherapy techniques provide the opportunity to maintain the quality of life by reducing the risk of complications. On the other hand, there are still unanswered questions, for example, the efficacy of population screening, the treatment modality that gives the best survival and quality of life in localized disease, the management of biochemical relapse and the pathology of hormone-refractory cancer.

EPIDEMIOLOGY

There has been an increase in both the incidence and mortality of prostate cancer and by 1990, it has become the second commonest cause of death in men in England and Wales (Majeed and Burgess, 1994). The incidence of prostate cancer in the UK in 1996 was 21 400 and the number of deaths from prostate cancer in 1998 was 9460 (National Statistics Office, 2002).

AETIOLOGY

The factors implicated for developing prostate cancer are depicted in *Table 1*. John et al (1995) found no conclusive evidence that vasectomy was a risk factor.

PATHOLOGY

Prostate cancer is a multifocal and heterogeneous disease. Most are adenocarcinomas that arise from high-grade prostatic intraepithelial neoplasia (PIN; Burton et al, 2000) which is present in 4.0–16.5% of needle biopsies and is strongly predictive of co-existing carcinoma, thus warranting a repeat biopsy (Wiley et al, 1997).

Many interesting and unusual morphological variants of prostate cancer have been identified but they account for less than 10% of cases. Their importance lies in the fact that they need to be recognized and differentiated from benign variants and that their clinical behaviour may differ from the usual prostate adenocarcinoma.

GRADING

The Gleason system (Gleason, 1992) is the most widely used. It gives a grade (1 to 5) to the most and the second most dominant architectural pattern of differentiation. The grade increases as the degree of differentiation decreases. If the most dominant pattern is graded 5 and the second most dominant pattern graded 4, this is described as a Gleason grade of 5+4, or a Gleason score of 9.

TABLE 1.
Risk factors implicated in the development of prostate cancer

Factor		Risk
Age		Advanced age
Ethnic origin		Afro-Caribbean origin
Positive family history		Early (<55 years) age
Diet	Fructose	Low
	Selenium	Low
	Vitamins D and E	Low
	Phytoestrogens	Low
	Lycopene	Low
	Fat	High

Mr Frank Lee is Research Fellow in Urology and **Mr Hitendra RH Patel** is Honorary Clinical Lecturer in Urology, Institute of Urology and Nephrology, University College London, London W1W 7EY

Correspondence to: Mr HRH Patel

TABLE 2.
The TNM staging system for prostate cancer

TNM	Description		
TX	Primary tumour cannot be assessed		
T0	No evidence of primary tumour		
T1	Clinically inapparent tumour, not palpable or visible by imaging	T1a	Incidental tumour found at transurethral resection of the prostate in which 5% or less of the resected tissue is cancerous
		T1b	As in T1a but more than 5% of the resected tissue is cancerous
		T1c	Cancer detected by needle biopsy of the prostate
T2	Palpable tumour confined to the prostate	T2a	Tumour involves one lobe
		T2b	Tumour involves both lobes
T3	Tumour beyond capsule (locally advanced)	T3a	Extracapsular extension
		T3b	Seminal vesicle involvement
T4	Tumour is fixed or is invading surrounding structures other than the seminal vesicles	T4a	Tumour invades bladder neck and/or external sphincter and/or rectum
		T4b	Tumour invades levator muscles and/or fixed to pelvic wall
NX	Regional lymph nodes cannot be assessed		
N0	No regional lymph node involvement		
N1	Metastasis in a single regional lymph node, maximum ≤ 2 cm		
N2	Metastasis in a single regional lymph node, maximum diameter between 2–5 cm; or multiple lymph node metastases, none >5 cm maximum diameter		
N3	Metastasis in a regional lymph node >5 cm in diameter		
MX	Presence of distant metastasis cannot be assessed		
M0	No distant metastasis		
M1	Distant metastasis	M1a	Involvement of non-regional lymph nodes
		M1b	Involvement of bone(s)
		M1c	Involvement of other distant sites

STAGING

A commonly used system is the TNM (tumour, node, metastasis) classification (*Table 2*). Clinical staging is the assessment of the extent of the tumour using digital rectal examination (DRE), PSA, and imaging modalities like transrectal ultrasound, computed tomography, magnetic resonance imaging or bone scan. Determination of the local extent of the tumour by DRE is referred to as T staging.

Pathological staging is more useful than clinical staging as a prognostic indicator because only the former can provide data on tumour volume, surgical margin status, extent of extracapsular spread and the involvement of the seminal vesicle(s) and pelvic lymph node(s). However, this information can only be obtained from radical prostatectomy specimen and not radiotherapy (no specimen). Therefore, accurate comparison between surgical and non-surgical treatment modalities continues to be limited.

DIAGNOSIS OF PROSTATE CANCER

This is made from history, examination and investigations (*Figure 1*). Early, organ-confined prostate cancer can be asymptomatic because the majority (70%) arise from the peripheral zone of the gland, away from the urethra. As the tumour grows, symptoms can develop as a result of local and/or metastatic effects (*Table 3*). In men presenting with lower urinary tract symptoms, it is important to exclude prostate cancer if the diagnosis and treatment would have a significant impact on the patient's survival.

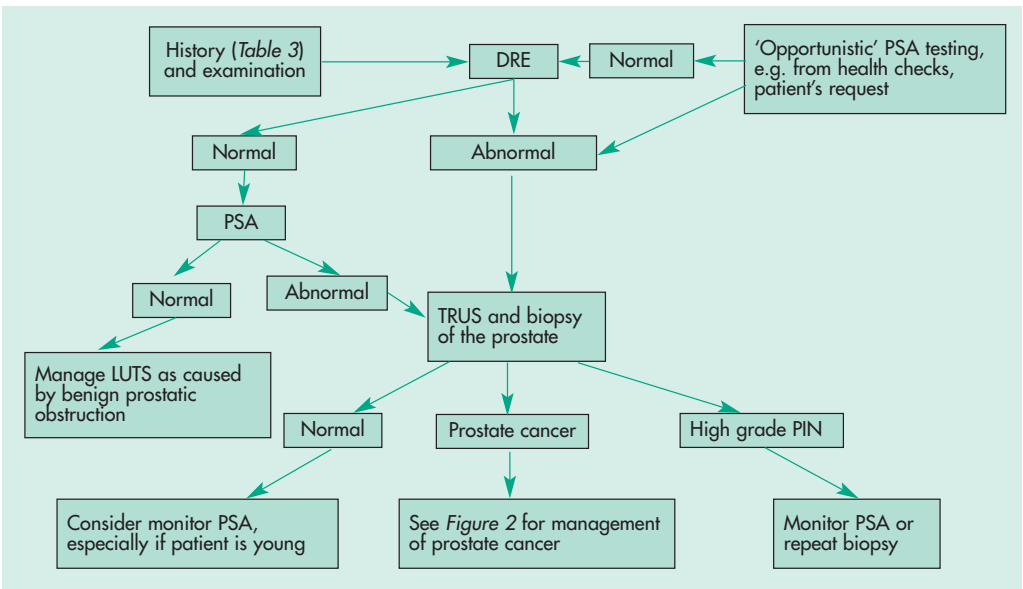


Figure 1. Diagnostic pathway for patients presenting with lower urinary tract symptoms or suspected prostate cancer. DRE = digital rectal examination; LUTS = lower urinary tract symptoms; PIN = prostatic intraepithelial neoplasia; PSA = prostate specific antigen; TRUS = transrectal ultrasound.

Digital rectal examination

DRE is the primary method for assessing the prostate. However, it is examiner-dependent and has inter-examiner variability (Smith and Catalona, 1995). Many early prostate cancers will be missed by DRE alone (Brawer et al, 1992).

PSA testing

This has revolutionized the diagnosis, staging and management of prostate cancer. PSA is a serine protease produced almost exclusively by the prostatic epithelium and periurethral gland in males. Although low concentrations are produced by the endometrium, breast tissue, adrenal and renal carcinoma, it is sufficiently organ-specific in clinical practice. However, it is not specific for prostate cancer because it can also be raised by manipulation (transrectal ultrasound, biopsy, cystoscopy), in urinary retention, prostatitis and benign prostatic hyperplasia. The latter can cause diagnostic dilemmas if the PSA is mildly elevated (4–10 ng/ml) as this can be the result of either benign prostatic hyperplasia and/or cancer. To improve PSA sensitivity and specificity, PSA density, PSA velocity, age-related PSA and the free/total PSA ratio have been used. All increase accuracy of diagnosing cancer, but the last method appears to be most promising (van der Cruijsen-Koeter et al, 2001).

Transrectal ultrasound and needle biopsy of the prostate

Although transrectal ultrasound can detect prostate cancer as a hypoechoic lesion, benign processes like prostatitis or infarction can have a similar appearance. Furthermore, not all prostate cancer is hypoechoic on ultrasound. The use of colour Doppler ultrasonography to detect the hypervascularity of cancer may improve its sensitivity. Nevertheless, transrectal ultrasound is essential in performing a systematic needle biopsy of the prostate (Littrup and Bailey, 2000). Complications of needle biopsy include haematospermia (45.5%), haematuria (23.6%) and low grade fever (4.2%). With the use of prophylactic antibiotics, the risk of developing septicaemia and prostatitis is less than 1% (Rietbergen et al, 1997).

Guidelines by the British Association of Urological Surgeons suggest PSA testing and needle biopsy should only be performed after proper counselling of suitable patients. It should not be used in those for whom it is inappropriate, e.g. in the very elderly or in those whose co-existing medical morbidity has already severely compromised life expectancy (Dearnaley et al, 1999). *Table 4* shows the chance of detecting cancer on prostatic biopsy after DRE and PSA results are known.

TABLE 3.
Symptoms of prostate cancer

Effects	Symptoms
Local effects (from growth of prostate cancer into neighbouring structures, e.g. prostatic urethra, ejaculatory ducts, neurovascular bundle innervating the corpora cavernosa, distal ureter)	Obstructive voiding symptoms, e.g. hesitancy, variable flow, terminal dribbling
	Irritative storage symptoms, e.g. urgency, frequency, nocturia, urge incontinence
	Haematospermia
	Decreased ejaculate volume
	Erectile dysfunction
	Symptoms of renal failure
Metastatic effect (from involvement of bone, pelvic lymphatic or venous drainage)	Bone pain
	Anaemia
	Lower limb oedema

If cancer is detected, the overall chance of organ confinement can be calculated using Partin's tables (using initial PSA, clinical staging and biopsy Gleason scores; Partin et al, 2001). Clinicians have been using these numbers to counsel patients when deciding upon curative treatment, e.g. radical prostatectomy.

TREATMENT OF PROSTATE CANCER

Early (localized) prostate cancer

Figure 2 gives a management pathway for early prostate cancer. This is organ-confined and if treated appropriately, offers the best chance of cure. There are three treatment options: watchful waiting, radical radiotherapy and radical prostatectomy. Watchful waiting is usually offered to men with low-grade, low-volume disease (<0.5 ml) who have a life expectancy of less than 10 years. Radical prostatectomy is the preferred option for younger and fitter men with the intention of curing an organ-confined disease on clinical staging. However, up to half of these men

TABLE 4.
The possibilities of detecting prostate cancer on needle biopsy of the prostate after DRE and PSA testing

DRE	PSA (ng/ml)	Chance of cancer on needle biopsy (%)
Normal	<4	6
Normal	>4	23
Abnormal	<4	15
Abnormal	>4	56

DRE = digital rectal examination; PSA = prostate specific antigen

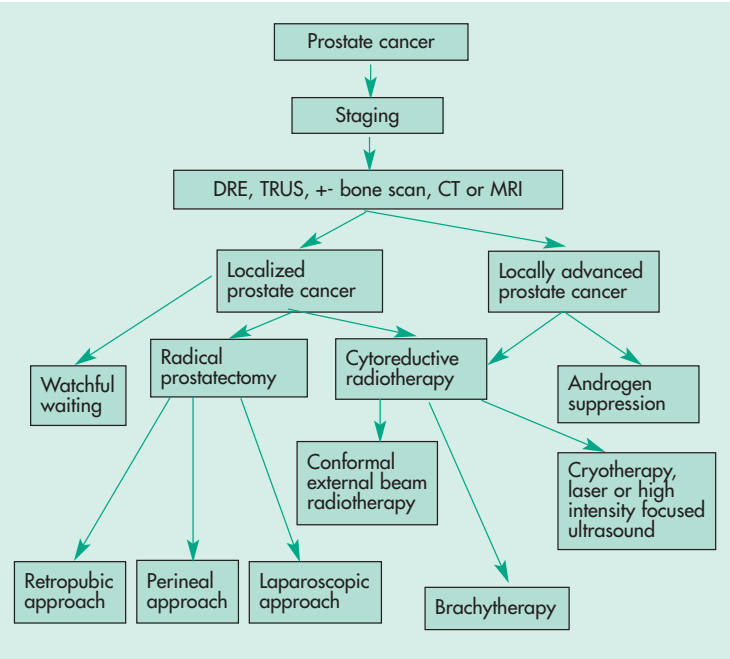


Figure 2. Management pathway for early (localized) and locally advanced prostate cancer. CT = computed tomography; DRE = digital rectal examination; MRI = magnetic resonance imaging; TRUS = transrectal ultrasound.

have extra-capsular disease on pathological staging, preventing a curative operation. Radical radiotherapy can be offered to any group of patients, but is more appropriate for surgically high-risk men. This can be delivered via external beam (conformal) irradiation or implantation of radioactive seeds (brachytherapy). It is usually combined with cytoreductive hormonal therapy (neoadjuvant and/or adjuvant androgen suppression). These decisions are not evidence based, but result largely from informed choices made by patients and their relatives, with assistance from the clinician. Fully informed patients are made aware of the potential complications from radical prostatectomy and radiotherapy (*Table 5*), as well as the side effects of medical therapy (*Table 6*).

While the difference in disease-free survival of all patients with localized disease among these three options was between 10 and 20% (Lu-Yao and Yao, 1997), for patients with poorly differentiated tumours, their 10-year disease-specific survival rate was higher after radical prostatectomy (Gerber et al, 1996).

TABLE 5.
Common potential complications after radical prostatectomy and radiotherapy

Complication	Radical prostatectomy	Radical radiotherapy
Erectile dysfunction	yes	yes, less common in radiotherapy
Urinary incontinence	yes	yes, less common in radiotherapy
Anastomotic stricture/ bladder neck stenosis	yes	yes
Bladder irritation	yes, usually transient	yes
Rectal irritation	no	yes

Locally advanced prostate cancer

Although radical prostatectomy (*Figure 2*) is probably inappropriate because of the unacceptably high local and distant recurrence rate, some urological surgeons may still consider this option in a few selected patients. Radical radiotherapy (with cytoreductive hormonal therapy) is unlikely to be curative but it will delay local progression. The remaining patients will receive androgen suppression with or without maximal androgen blockade.

Maximal androgen blockade: This involves suppressing testosterone production from the testes (by orchidectomy or luteinizing hormone-releasing hormone agonists) and adrenals (by antiandrogens), which in turn inhibits the stimulation of prostatic cells (cancerous and benign). The theory is attractive and resulted in years of conflicting reports on its efficacy, including the statistical validity of the studies involved. A meta-analysis showed a modest 2–3% improvement in 5-year survival using maximal androgen blockade compared with castration (medical or surgical) alone (Prostate Cancer Trialists Collaborative Group, 2000).

Metastatic prostate cancer

The main treatment for this is androgen suppression (*Figure 3*). About 70% will respond. Apart from bilateral orchidectomy, a number of agents are available (*Table 6*). Unfortunately, almost all of these patients will relapse after a period and develop hormone-refractory disease (*Figure 2*). There is no consensus in the management of this difficult situation. When this happens in patients who are on maximal androgen blockade, it is worth stopping the antiandrogen as up to 50% of patients will show a drop in their PSA, albeit transient. Second-line hormonal therapy entails a cocktail: steroid plus stilboestrol (after breast bud irradiation) plus aspirin or warfarin (to reduce thromboembolic events).

Chemotherapy has been tried, although the results with single agents, e.g. estramustine or vinblastine, have been relatively disappointing. However, the early results using taxanes, e.g. paclitaxel, in combination with other agents, e.g. estramustine, were promising (Murphy, 1999) with half of the patients showing a drop in PSA.

If patients do not respond to second-line treatment, the prognosis is poor. Renal failure can ensue as a result of distal ureteric undermining

by the encroaching prostate cancer. The priority now is to decide with the patient and his relatives whether to proceed to active intervention (percutaneous nephrostomy with or without antegrade stenting) or palliative management.

SCREENING

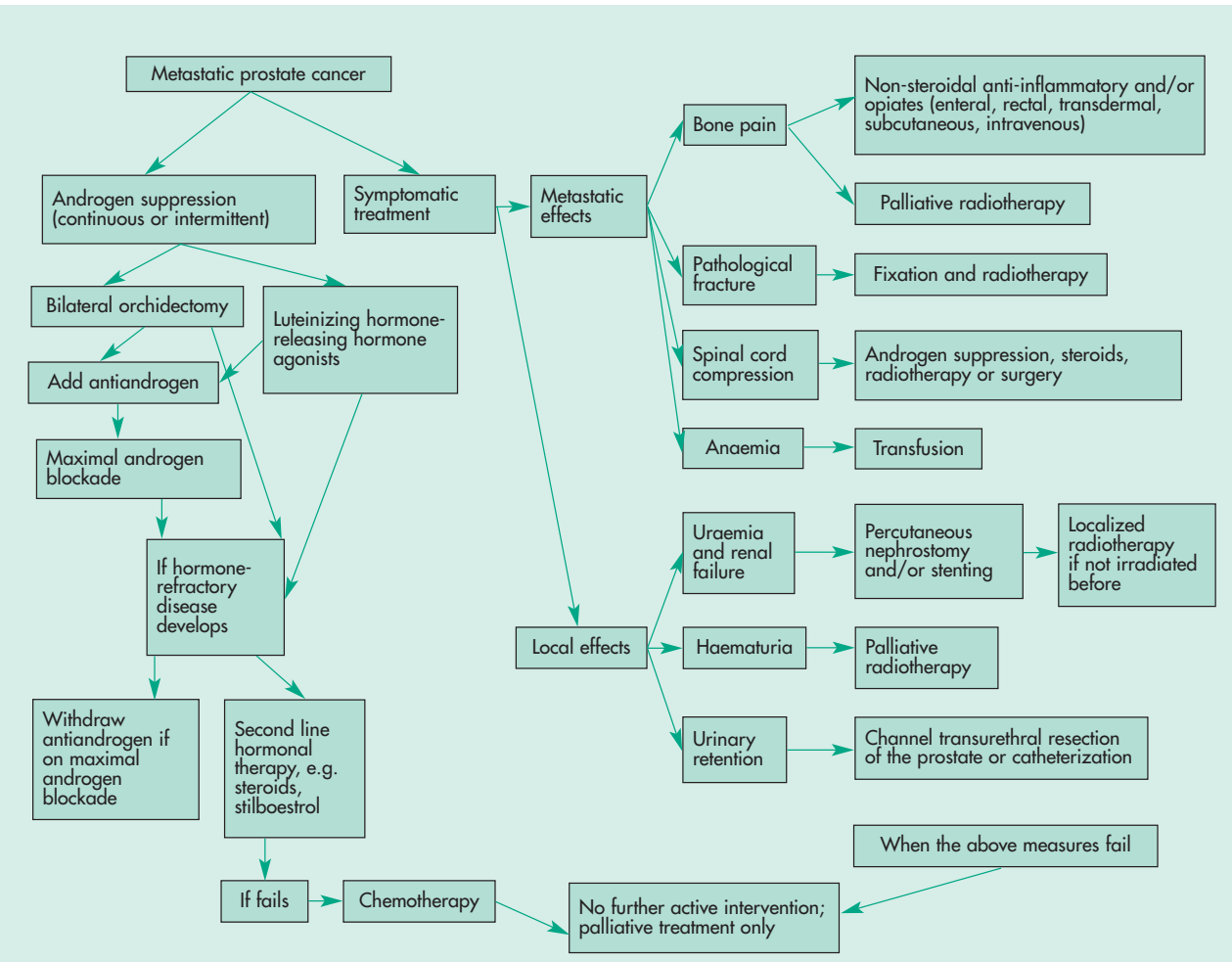
Early detection and aggressive treatment is the only chance to cure prostate cancer. PSA-based screening advances the diagnosis by 6–10 years and results in a significant stage reduction. However, the survival benefit and the effect on the quality of life from population screening are at present unknown. There is also concern about over-diagnosis and current UK practice has recommended that its role must be subjected to valid controlled trials before instigation.

Controversially, the American Cancer Society and the American Urological Association have ignored the fact that no valid trial exists to show screening for prostate cancer reduces prostate cancer-related deaths. They have instigated guidelines to offer all

TABLE 6.
Common side effects of medical treatment for advanced prostate cancer

Agent	Side effects
Luteinizing hormone-receptor agonists	Hot flushes
	Erectile dysfunction
	Decreased libido
	Osteopenia
	Anaemia
Non-steroidal antiandrogens	Gynaecomastia
	Diarrhoea
Cyproterone acetate	Fluid retention
	Erectile dysfunction
	Hepatic dysfunction (rare but widely known)
Stilboestrol	Gynaecomastia
	Erectile dysfunction
	Cardiovascular toxicity including thromboembolism

Figure 3. Management pathways for metastatic prostate cancer.



men ≥50 years old, and men ≥45 years old in high risk groups an annual PSA and DRE (Smith et al, 2001).

ON THE HORIZON

Apart from research on therapeutic agents to improve the prognosis of advanced prostate cancer (*Table 7*), there are controlled trials investigating the benefits of screening and the long-term outcome of various treatments for localized disease. After these long-term studies are completed, important questions concerning treatments may be answered.

TABLE 7.
Agents being studied for the treatment of prostate cancer

Agent	Example
LHRH receptor antagonist	Abarelix
17,20 lyase inhibitors (MAB in a single agent)	Abiraterone acetate
Endothelin receptor antagonist	ABT-627
Angiogenesis inhibitor	Angiostatin
	Thalidomide
Cell-cycle inhibitors	DNA synthesis inhibitor suramin
Combined (type 1 and 2) 5 alpha-reductase inhibitor	Thymidine kinase ganciclovir adenovirus
	Cytosine deaminase gene product
Adnovirus/suicide gene therapy	
Immunotherapy	Granulocyte-monocyte-colony stimulating factor vaccine
	Allovax
	Dendritic cells to present PSA to T cells
Apoptosis agonists	Anti-sense Bcl-2 oligonucleotides

LHRH = luteinizing hormone-releasing hormone; MAB = maximal androgen blockade; PSA = prostate specific antigen

KEY POINTS

- The value of population screening in reducing mortality and its effects on quality of life have not yet been established.
- The deficiency of digital rectal examination has been improved by the use of prostate specific antigen (PSA) testing, transrectal ultrasound and biopsy of the prostate.
- A total PSA threshold at 4.0 ng/ml remains the strongest predictor for prostate cancer.
- Under-grading of needle biopsy specimens is common.
- An estimated 35–50% of patients develop a biochemical relapse within 10 years after radical prostatectomy because the tumour was not organ confined on pathological staging, despite the prediction on preoperative clinical staging.
- It has been found in several studies that early androgen suppression in patients with asymptomatic metastatic disease is associated with less progression and fewer complications like ureteric obstruction or pathological fracture.
- Before PSA testing, needle biopsy and any treatment options, patients (and preferably their relatives) must be fully counselled and informed.

CONCLUSIONS

More knowledge is required for the identification of organ-confined cancer that is potentially aggressive and life-threatening which require prompt and curative treatment. The outcome of metastatic and hormone-refractory disease remains poor and a better understanding of their pathology is necessary. HM

Conflict of interest: none.

Brawer MK, Chetner MP, Beatie J, Buchner DM, Vessella RL, Lange PH (1992) Screening for prostate carcinoma with prostate specific antigen. *J Urol* **147:** 841–5

Burton JL, Oakley A, Anderson JB (2000) Recent advances in the histopathology and molecular biology of prostate cancer. *BJU Int* **85:** 87–94

Dearnaley DP, Kirby RS, Kirk D, Malone P, Simpson RJ, Williams G (1999) Diagnosis and management of early prostate cancer. Report of a British Association of Urological Surgeons Working Party. *BJU Int* **83:** 18–33

Gerber GS, Thisted RA, Scardino PT et al (1996) Results of radical prostatectomy in men with clinically localized prostate cancer. *JAMA* **276:** 615–9

Gleason DF (1992) Histologic grading of prostate cancer: a perspective. *Hum Pathol* **23:** 273–9

John EM, Whittemore AS, Wu AH et al (1995) Vasectomy and prostate cancer: results from a multiethnic case-control study. *J Natl Cancer Inst* **87:** 662–9

Littrup PJ, Bailey SE (2000) Prostate cancer. The role of transrectal ultrasound and its impact on cancer detection and management. *Radiol Clin North Am* **38:** 87–113

Lu-Yao GL, Yao SL (1997) Population-based study of long-term survival in patients with clinically localised prostate cancer. *Lancet* **349:** 906–10

Majeed FA, Burgess NA (1994) Trends in death rates and registration rates for prostate cancer in England and Wales. *BJU Int* **73:** 377–81

Murphy GP (1999) Review of phase II hormone refractory prostate cancer trials. *Urology* **54:** 19–21

National Statistics Office (2002) *StatBase dataset.* National Statistics Office, London http://www.statistics.gov.uk/statbase/xsdataset.asp?vlnk=3352&B4.x=35&B4.y=8 Accessed 9 July 2002

Partin AW, Mangold LA, Lamm DM, Walsh PC, Epstein JI, Pearson JD (2001) Contemporary update of prostate cancer staging nomograms (Partin Tables) for the new millennium. *Urology* **58:** 843–8

Prostate Cancer Trialists Collaborative Group (2000) Maximum androgen blockade in advanced prostate cancer: an overview of the randomised trials. *Lancet* **355:** 1491–8

Rietbergen JB, Kruger AE, Kranse R, Schroder FH (1997) Complications of transrectal ultrasound-guided systematic sextant biopsies of the prostate: evaluation of complication rates and risk factors within a population-based screening program. *Urology* **49:** 875–80

Smith DS, Catalona WJ (1995) Interexaminer variability of digital rectal examination in detecting prostate cancer. *Urology* **45:** 70–4

Smith RA, von Eschenbach AC, Wender R (2001) American Cancer Society guidelines for the early detection of cancer. Update of early detection guidelines for prostate, colorectal and endometrial cancers. *CA Cancer J Clin* **51:** 38–44

Wiley EL, Davidson P, McIntire DD, Sagalowsky AI (1997) Risk of concurrent prostate cancer in cystoprostatectomy specimens is related to volume of high-grade prostatic intraepithelial neoplasia. *Urology* **49:** 692–6

van der Cruijsen-Koeter IW, Wildhagen MF, de Koning HJ, Schroder FH (2001) The value of current diagnostic tests in prostate cancer screening. *BJU Int* **88**: 458–66