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Review

Diagnosis, management and screening of early localised prostate cancer

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Diagnosis, management and screening of early localised prostate cancer

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NHS R&D HTA Programme

The overall aim of the NHS R&D Health Technology Assessment (HTA) programme is to ensure that high-quality research information on the costs, effectiveness and broader impact of health technologies is produced in the most efficient way for those who use, manage and work in the NHS. Research is undertaken in those areas where the evidence will lead to the greatest benefits to patients, either through improved patient outcomes or the most efficient use of NHS resources.

The Standing Group on Health Technology advises on national priorities for health technology assessment. Six advisory panels assist the Standing Group in identifying and prioritising projects. These priorities are then considered by the HTA Commissioning Board supported by the National Coordinating Centre for HTA (NCCHTA).

This report is one of a series covering acute care, diagnostics and imaging, methodology, pharmaceuticals, population screening, and primary and community care. It was identified as a priority by the Diagnostics and Imaging Panel (see inside back cover).

A considered decision was taken to commission two similar reports in the area of prostate cancer as an experiment during the initial funding phase of the HTA programme. The aim was to explore the consistency of systematic reviews when commissioned from research teams with different backgrounds and research expertise. This report has, as one of its main focuses, early localised prostate cancer, whereas the related report [Chamberlain J, *et al.* The diagnosis, management, treatment and costs of prostate cancer in England and Wales. *Health Technol Assess* 1997;**1**(3)] provides a strong link with health economic issues. The two reports provide an excellent overview of this field and will greatly enhance the knowledge base from which future decisions in this field will benefit.

The views expressed in this publication are those of the authors and not necessarily those of the Standing Group, the Commissioning Board, the Panel members or the Department of Health.

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List of abbreviations

AAH	atypical adenomatous hyperplasia
ACS–NPCDP	American Cancer Society – National Prostate Cancer Detection Project
ACT	alpha$_1$-antichymotrypsin
ACTH	andrenocorticotropic hormone
BOO	bladder outlet obstruction
BPH	benign prostate hyperplasia
CDI	colour Doppler imaging
CI	confidence interval
CT	computed tomography
DRE	digital rectal examination
EORTC	European Organisation for Research in Treatment of Cancer
ERSPC	European Randomised Study of Screening for Prostate Cancer
GP	general practitioner
LH–RH	luteinising hormone–releasing hormone
MRC	Medical Research Council
MRI	magnetic resonance imaging
NPV	non-positive predictive value
PCR	polymerase chain reaction
PIN	prostatic intra-epithelial neoplasia
PIVOT	Prostate cancer Intervention Versus Observation Trial
PLCO	Prostate, Lung, Colon, Ovary trial
PPV	positive predictive value
PSA	prostate specific antigen
PSAD	prostate specific antigen density
RCT	randomised controlled trial
TNM	pathological staging of tumours: T – primary; N – regional nodes; M – metastatic
TRUS	transrectal ultrasound
TURP	transurethral resection of the prostate
UICC	International Union against Cancer
VACURG	Veterans Administration Cooperative Urological Research Group

Chapter 1

Summary

The incidence of prostate cancer is rising worldwide, caused mainly by demographic factors, particularly the increasingly elderly population and, more importantly, the increasing number of cases identified following prostate specific antigen (PSA) testing. It is commonly quoted that many more men die **with** prostate cancer than **of** it. Autopsy/post-mortem studies show that while a very high proportion of elderly men have histological evidence of the disease, a much smaller proportion develop clinically apparent cancer. The natural history of prostate cancer is poorly understood, but progression appears to be related to stage and grade of tumour.

Prostate cancer can be diagnosed by digital rectal examination (DRE), serum PSA test, and/or transrectal ultrasound (TRUS), with confirmation by biopsy. Each test identifies a proportion of cancers, with higher rates of detection when they are used in combination. The tests are also used to determine which tumours are localised within the prostate and are, thus, potentially treatable. Unfortunately, clinical staging is unreliable, with approximately one half of all tumours upstaged following surgery.

Three major treatment options are available for localised prostate cancer: radical prostatectomy, radical radiotherapy and conservative management (involving monitoring and treatment of symptoms). Although radical treatment rates are rising, good quality evidence concerning their comparative effectiveness and cost-effectiveness is lacking. Observational studies of highly selected patient groups suggests that there may be a slightly lower mortality rate following radical treatments compared with conservative management, but there has been very little research into treatment complications and quality of life of men after any of the treatments.

In the past, investigations of prostate cancer were reserved largely for patients exhibiting symptoms, but the introduction of the PSA test has opened up the possibility of screening healthy men for the disease. Observational studies suggest that DRE and PSA, combined with TRUS and biopsy, can identify localised prostate cancer in 3–5% of men, although the tests do result in a number of false positives and negatives.

Major questions remain concerning the natural history of the disease, potential costs (financial, social and psychological) of a screening programme, and the effectiveness and cost-effectiveness of treatments for localised disease. The lack of good quality data and the strength of these concerns means that population screening for prostate cancer cannot be recommended.

Chapter 2

Epidemiology

Prostate cancer has received increasing media attention, partly through the publicity surrounding a number of famous people with the disease, including Frank Zappa, Telly Savalas, Bob Dole, François Mitterand, but also following media reports about the increasing availability of simple diagnostic tests such as PSA. The natural history and progression of the disease are, however, poorly understood and documented. There is a large discrepancy between the incidence of the disease and mortality from it, with many more men dying with the disease than of it. It is likely that prostate cancer is a disease with a long natural history, with progression commonly related to stage and grade of tumour and lack of differentiation. Sex hormones, genetic factors and some environmental agents have been implicated in causing the development of prostate cancer. The incidence worldwide is rising, although this is probably related to increasing rates of detection, diagnosis, and reporting as well as to increases in the elderly population rather than to the disease itself. In particular, there are increasing numbers of cases defined and detected following PSA testing.

Prostate cancer is recognised to be a considerable and increasing health care problem in a wide range of countries, including, for example, Hungary,[1] Canada,[2] Bulgaria,[3] the Nordic countries,[4] and Australia,[5] as well as the USA and countries of the EU.

In the last decade, clinical cases of prostate cancer have more than doubled. In part, this has been due to the ageing of the population – prostate cancer is acknowledged to be a disease associated with increasing age (see below) – and improvements in medical care which eliminate competing causes of death. Increases have, however, far outstripped simple population ageing. It has been suggested that an unidentified carcinogen may be present in increasing amounts, although more likely reasons are the dramatic improvements in diagnostic equipment – particularly developments in PSA testing and needle biopsy, increased rates of transrectal resection of the prostate (TURP), and increased public awareness bringing more men forward for diagnosis.[6–8]

It has been claimed that prostate cancer is a serious problem, but that it is mostly a disease of elderly men and has a relatively small impact on premature death.[9] It is often stated that men are more likely to die **with** prostate cancer than **of** it.

Natural history

The prostate is a gland which produces and is affected by multiple hormones, particularly testosterone and dihydrotestosterone.[10] Adenocarcinomas represent over 95% of prostate cancers.[11,12] Prostate cancer is often multicentric within the gland, and the tumour shows a strong predilection for perineural invasion. Eventually the tumour can invade and perforate the capsule, allowing invasion into periprostatic tissues.[11] The majority of cancers occur in the peripheral portions of prostate,[13–15] whereas for benign prostatic hyperplasia (BPH), the transition zone is more commonly affected. Some 15% of prostate cancers are, however, found within the transition zone, and a further 5% in the central portion.[11]

The natural history of prostate cancer is poorly documented, but a number of factors arise persistently. In particular, it is well known that histological evidence of the disease far outweighs the number of clinically diagnosed tumours (see below). In addition, progression has been found to be typically related both to stage and grade of tumour, as well as loss of differentiation.

It is common in the literature to find prostatic cancers defined as ‘latent’ or ‘clinical’ tumours, with the implication that these might be distinctive types.[16] Research by McNeal and colleagues, however, has suggested that prostate cancer is probably a single disease which may have an extremely long natural history.[16] Thus the apparent unpredictability of behaviour in prostate cancer need not imply the existence of innocuous or ‘latent’ cancer, it may be a function of the large proportion of tumours under 1 ml in volume which would remain clinically silent. In turn, this may be caused by the slow rate of growth in the early phase of the development of prostate cancer.[16] Carcinomas seen at necropsy, clinically-detected carcinomas and metastatic carcinomas may therefore represent different phases along the biological continuum of a single type of cancer.[16]

It has been suggested that prostatic intraepithelial neoplasia (PIN) and atypical adenomatous hyperplasia (AAH) may represent a precancerous state and could be important in the diagnosis of early prostate cancer. Evidence is, however, inconclusive.[17]

Progression is poorly understood, with variable rates reported in different studies, together with the finding that progression is not inevitable within the lifetime of a patient with histological evidence of the disease.[18] No spontaneous regression of prostate cancer has been reported, and growth is usually described to be related to grade, but also to other factors including tendency to invade locally and metastasise.[13] Host factors influencing tumour behaviour have not been clearly identified, although age-related hormonal changes and other factors have been implicated (see below).

The natural history of prostate cancer has been studied prospectively over 7 years within one health district in the UK. All men with histologically-confirmed prostate cancer and negative bone scans were managed by conservative management (including TURP for relief of urinary symptoms). Local tumours increased to palpable dimensions in 100 (84%), and metastases developed (detected by bone scan) in 13 (11%). Five died of prostate cancer (4%). Actuarial survival rates at 5 and 7 years were 80% and 75%.[19] Thus, only a relatively small proportion of men diagnosed with non-metastatic ‘clinical’ prostate cancer progressed to metastases and death from prostate cancer.

A pooled analysis of 828 patients also undergoing expectant management was undertaken, utilising a Cox regression analysis to determine factors influencing survival.[20,21] Grade was identified as the most specific risk factor.[20,21] Ten years after diagnosis, disease-specific survival was 87% for men with grade 1 or 2 tumours and 34% for those with grade 3 lesions. This assessment was confirmed in two further studies, one of which indicated that tumours of advanced clinical stage are more likely to be high grade than low grade,[18] and another which implicated extent as well as grade of disease in tumour progression.[22]

There is, however, uncertainty concerning the extent to which grade change according to stage results from de-differentiation of an initially well-differentiated tumour or from progressive overgrowth of a small, poorly differentiated component in the initial lesion.[18]

Loss of differentiation was identified as an important factor in progression in another study which also implicated the size of the tumour. One hundred unselected prostates with carcinoma removed at necropsy and 38 removed at radical prostatectomy were evaluated.[16] Metastases were only associated with tumours larger than 4 ml. Loss of differentiation was associated with tumour volume, and only Gleason grades 4 or 5 metastasised. It was then suggested that the capacity to metastasise probably develops only in tumours which have grown larger than 1 ml and acquired poorly differentiated areas.[16]

This study further supports the finding by McNeal and colleagues that progression is linked to loss of differentiation which, in turn, is linked to increasing volume.[16]

Size of the problem

In the USA, prostate cancer is reported to be the most frequently diagnosed male malignancy, with between 84,889[7] and 132,000[23] new cases per year, and a lifetime risk of 9–11% of developing the disease.[8,23,24] It is estimated that some 32,000 men died of prostate cancer in the USA in 1991, with the disease being the second greatest cause of cancer death in men after lung cancer.[25] In 1993, the American Cancer Society predicted that there could be 165,000 new cases and 36,000 deaths from prostate cancer per year.[6]

Within the EU, there are an estimated 85,000 new cases of prostate cancer diagnosed every year – 13% of cancers in men.[26] In addition, 9% of all cancer deaths among men are reported to be caused by prostate cancer.[26] Deaths in the EU caused by prostate cancer are estimated at approximately 35,084 per year – 8.6% of all male deaths due to cancer.[7]

In England and Wales in 1987, there were 10,837 new cases of prostate cancer. In 1991, prostate cancer ranked second to lung cancer in mortality from malignant disease in men, with 8570 prostate cancer deaths.[23,24]

The pattern of clinical presentation of prostate cancer varies between different parts of the world. In the USA, 40% of patients exhibit extra capsular spread by time of diagnosis.[25] In the EU, this figure is approximately 50–60%,[7] and in the UK is suggested to be as high as 75%, with 50% having metastastatic disease.[23,27]

A number of studies have been undertaken to estimate the prevalence and incidence of prostate cancer. Some of these studies have focused on histological rates, while others have concentrated on determining rates of clinical evidence of the disease.

Prevalence

The prevalence of prostate cancer is clearly related to age.[28] The age-specific prevalence of microscopic (histological) prostate cancer far exceeds the prevalence of the clinically recognised disease.[6,18,29] It has been calculated, for example, that the prevalence of prostate cancer at death (i.e. histological evidence) for a 60-year-old man is 32%, but the prevalence in living men (of clinically-defined disease) is approximately 4%.[30]

There is broad agreement between studies concerning the prevalence of histological prostate cancer, although precise estimates are somewhat different. It is suggested, for example, that 15–30% of men aged over 50 years have histological evidence of prostate cancer and that, by the age of 80 years, this prevalence rises to 60–70%.[10,29] In another study, histological evidence of disease is suggested to reach 90% in men over 90 years.[6] A review of various necropsy studies shows that foci of microscopic, well-differentiated prostatic adenocarcinoma can be found in 30–40% of men aged 75 years and over.[23]

There is some variation, however, in the reported prevalence of prostate cancer in the general population. In part this is because of the variable definition of the disease, including incidentally discovered prostate cancer following investigations for other urinary conditions and detected disease in screened populations (‘PSA-defined disease’).

In the UK, men aged between 55 and 70 years in one general practitioner (GP) practice were invited to attend a health check.[31] Of the 82% who attended, 472 (58%) were screened using PSA and DRE, with TRUS and biopsy where appropriate.[31] Seven prostate cancers were identified (a prevalence rate of 1.5%), and all were organ confined.[31]

A number of similar studies have been carried out in the USA. Here, the sampling frames are somewhat different, with men volunteering for screening or testing following press advertisements,[32–35] or as part of a cancer detection study.[36] These studies have tended to report higher prevalences than the UK study described above (ranging from approximately 2%[34,37] to 5.8%,[32] but with the majority between 3% and 4%[25,33,35,36]). In part, the higher figures are probably due to inevitable biases in these populations. Those responding to advertisements are likely to be more aware of health issues than the bulk of the population, they may also be healthier (the infirm are unlikely to respond to advertisements), and may be richer or of higher social class.

The prevalence rate is, of course, dependent on the method of detection used. For example, Catalona and colleagues reported detection rates of 3.2% using DRE alone, 4.6% with PSA alone, and 5.8% using a combination of DRE and PSA.[32]

A combined meta-analysis of prostate cancer screening criteria assumed that clinical prostate cancer usually involved tumours > 0.2 cc, non-diploid, with a high Gleason score, and in the peripheral zone of the gland.[38] On the basis of this, the authors calculated the prevalence of clinical prostate cancer to be 20% of that found in autopsy studies – for example, 5.5% in those aged 5–59 years; 8%, 60–69 years, and 10.3%, 70–79 years.[38]

Only a small number of studies have investigated the prevalence of prostate cancer among men attending urology clinics and suspected of bladder outlet obstruction (BOO). Of 234 BOO patients attending one clinic, 46 (20%) were found to have a PSA level in excess of 10 ng/ml, confirmed as prostate cancer following examination of TURP specimens.

Incidence

The incidence of a condition refers to the number of new cases identified in a given population over a defined period – usually one year.

Between 1978 and 1982, the incidence of prostate cancer in the EU has been suggested to be approximately 55 per 100,000 per annum.[7] In another study, limited variations were found across Europe, but the highest incidence rates were identified in Germany, France, Belgium and the Netherlands, and the overall incidence in men was approximately 40 per 100,000 person years.[26]

In the USA, rates are considerably higher, with incidence rates calculated from 30,413 men in the Detroit SEER programme from 1973–1991 reported to be 102 per 100,000 per annum among whites in 1988, and 141 among blacks, increasing to 178 and 218 by 1991.[12]

Incidence is clearly related to age. In the USA, the rate for white men aged 50–54 years between 1969 and 1971 was 53 per 100,000.[39] For men aged 60–64 years this was 127, and for those aged 70–74 years 430 per 100,000.[39]

Incidence rates are reported to be increasing rapidly.[29] For example, between 1979 and 1990 in France, the incidence rate for prostate cancer in Isère increased from 22.1 to 45.0 cases per 100,000 men, representing a mean increase per year of 6.3%, with the largest increases from 1985 onwards.[40] The incidence of cases with metastases at diagnosis remained stable. During this time, PSA testing began, and TRUS was used in earnest.[40]

Further evidence comes from the USA where, between 1983 and 1989, the age-adjusted incidence rate for prostate cancer was found to have increased by an average of 6.4% per year, from 276 to 383 per 100,000.[41] The increase was evident in men of all ages studied. Localised disease accounted for two-thirds of the growth in incidence rates. Interestingly, geographical differences in incidence within the USA increased over time – by 1989, Seattle had a rate more than twice that for Connecticut.[41]

Mortality rates

Prostate cancer is responsible for about 3% of male deaths and 13% of male cancer deaths in the USA. About 80% of clinical diagnoses are made after the age of 65 years, and 90% of deaths occur after 65 (median, 77 years).[41] The ratio of clinical incidence to mortality diminishes progressively from about 8 (at ages 50–54 years) to 4 (at ages 75–79 years).

Mortality rates appear to vary between countries. Age-adjusted death rates in the USA in 1988, for example, were estimated to be 15.7 per 100,000 and in Japan 3.5 per 100,000.[10] In the EU, a mortality rate of between 12[26] and 22.6 per 100,000 person years has been suggested. The cumulative lifetime risk up to the age of 74 years has been estimated at 3.9% and the cumulative mortality at 1.2%.[7] For a 50-year-old US man with a life expectancy of 25 years, the lifetime risks of microscopic, clinical or fatal prostatic cancer have been estimated at 42%, 9.5% and 2.9%, respectively.[18]

Although it has been shown above that there have been significant increases in incidence, there is some conflicting evidence concerning mortality rates. The study cited above from the USA indicated that there was little variation across the country in terms of mortality, and that mortality rates had not changed appreciably between 1983 and 1989.[40,41] Other authors claim, however, that mortality has increased by 16%.[8]

Aetiology and risk factors

There are a number of wide ranging reviews of the evidence concerning aetiology and risk factors.[42–44] This section provides a summary of the strongest evidence concerning aetiology.

In general, the agents which cause the initiation of prostate cancer are unknown.[10,18] A small number of risk factors have been identified in studies with sufficient power, but this area is characterised by a large number of small studies, often producing conflicting or inconclusive results.

It is most likely that prostate cancer results from a complex interplay between age, endogenous hormones, genetic factors[10,18] and environmental influences, including dietary fat.[29,42]

Hormones

Sex hormones have been linked with prostate cancer, but the evidence remains inconclusive. Steroid hormone receptors are found in prostate cancer, and oestrogen therapy has been found to be effective in treating prostate cancer, indicating that hormones probably play an important role and higher levels of testosterone and dihydrotestosterone are found in cancerous prostatic tissue than in the normal prostate gland.[45]
In addition, the incidence of prostate cancer in castrated men is very low.[42]

A number of studies have been conducted to investigate links between sexual activity and prostate cancer, but their results are not conclusive and are confounded by factors such as fertility being measured by the number of children fathered and sexual activity linked to marriage.[23,42,45]

The involvement of hormones in prostate cancer development makes the determination of risk factors difficult because of the interaction between several hormones – testosterone, 5-α reductase, sex hormone binding globulin, and oestrogen – as well as environmental factors such as diet and smoking.[42]

Genetic factors/family history

A number of studies have established that genetic factors are involved in some cases of prostate cancer. One author contends that these are of two types: hereditary prostate cancer which is distinguished by early age at onset and autosomal dominant inheritance within families;[43,46] and familial prostate cancer in which members of the same family have the disease. Hereditary prostate cancer results from a gene and confers a greatly increased susceptibility to the disease.[46] It may account for a substantial amount of early onset disease, and overall about 9% of prostatic cancer.[46]

Family history of prostate cancer has been identified in many studies as a clear risk factor.[6,11,24,42,45,47–50] Odds ratios of 2 or more for men with an affected first-degree or second-degree relative have been found, with the risk increasing with the total number of affected family members.[46,49,51] Family history has been reported by as many as 10% of men with prostate cancer.[48]

It has been suggested that familial prostate cancer may be a different, more aggressive form of the disease than that found in the general population, primarily because it tends to occur at early ages and accounts for a substantial fraction of the disease in younger men.[46,51]

Increased risk has also been associated with a family history of breast cancer.[23,42]

The increased level of risk conferred by the familial/inherited disease has led some to call for screening or early detection programmes for men with a father or brother with the disease.[49,52]

Ethnicity/race

No studies of variations in prostate cancer rates between ethnic groups have been conducted in the UK, although there is considerable evidence of other national and international variations in the clinical diagnosis of prostate cancer.[45] It is generally accepted that there is little variation in the prevalence of microscopic evidence of prostate cancer around the world, but that there appear to be considerable differences in the rates of progression to clinically evident disease. This is further shown by migrants moving to higher risk areas acquiring the local incidence rate.[6,42]

International and national incidence rates for clinically-evident prostate cancer are considerable. For example, the highest incidence rates are observed among blacks in the USA (100.2 per 100,000), followed by whites in the USA (51.9 per 100,000) and Sweden (44.4 per 100,000), with the lowest rates among Japanese men.[11,24,45] Limited variations have been found across Europe, but the highest incidence rates are in Germany, France, Belgium and the Netherlands.[26] Prostate cancer is rare in Asia.[6,29]

Within the USA, a number of studies have examined differences between ethnic groups. By 1990, while the overall incidence had risen, the difference between ethnic groups was higher than expected (163.6 per 100,000 for blacks and 128.5 per 100,000 for whites).[53] Incidence rates have been found to vary by 120-fold between Chinese- and African-American men living in San Francisco.[42]

Particular concern in the USA has focused on the differences between reported rates of prostate cancer in blacks and whites. It is generally stated that African-American men have higher rates of prostate cancer than Caucasians. A number of reasons have been put forward. It is suggested, for example, that black men seem to have larger volume cancers – ones which are thought to progress more rapidly to become clinically evident,[42] and that they tend to have more poorly differentiated tumours.[16,54] They may also have a much higher rate of invasive cancer.[24] The mortality rate among African-American men from prostate cancer is two to three times higher than among Caucasian men.[55]

An age-race interaction was also reported in an analysis of 914 patients with stage B and C [T2, T3] prostate cancer treated with external beam radiation from the Connecticut SEER Tumour Registry data base.[56] Patients aged 60 or younger had a 5-year survival rate of 72% compared to 61% for those over the age of 60 ($p = 0.06$). When stratified by race, white patients had a 63% 5-year survival rate versus 47% in black patients ($p = 0.02$). It was considered that this result may be due to black patients presenting with higher stage disease than whites. Both races had similar stage and grade of disease at treatment but it is important to note that the number of blacks in this series was small (47 blacks, 867 whites).[56]

There may be structural reasons for the apparent differences between ethnic groups. The proportion of black men who receive radical prostatectomy has increased over time, but has lagged behind whites, and it has also been discovered that watchful waiting is more often chosen as a therapy for black men – although reasons for this are unknown.[53] Differences in socio-economic status may be involved,[42] and racism cannot be discounted.

There is limited evidence from other countries to confirm these US findings. A case control study in Canada, for example, indicated that men of British descent were at higher risk than those from the Ukraine.[47] Further research is required to establish reasons for real or structural differences which might exist between ethnic groups.

Environmental and other factors

Relationships between a disease and dietary factors are often complex and difficult to disentangle.[42] A number of dietary factors do, however, appear to be linked to prostate cancer, particularly fat and fibre intake.

The clinical incidence of prostate cancer is generally higher in 'western' societies. It has been found that prostate cancer deaths are highly correlated with total fat intake, as with breast cancer, particularly animal rather than vegetable fat. Overall, dietary fat seems to be associated with a higher risk for developing prostate cancer, with relative risks reported of 1.6–1.9 and odds ratios as high as 3.6 for high saturated fat intake.[23,24,57] Similarly, when plasma lipid levels were measured in cases and controls, the relative risk for men with high levels of plasma alpha-linolenic acid was 3.0.[58] How dietary fat is related to higher risk is unclear, but it is hypothesised that dietary patterns can alter the production of sex hormones which influence the development of prostate cancer.[42,45]

The evidence concerning other dietary factors is confusing, with soya intake suggested as a possible protective factor,[59] and deficiency in vitamin A leading to increased risk of prostate cancer.[42]

A number of studies have examined exposure of various chemicals and the relative risk of developing prostate cancer. The only factor to be identified consistently is cadmium.[23,42,45] Increased risks have been suggested with the rubber industry,[42,45] radiation exposure,[23] farm working,[42] newspaper industry and plumbing.[42] These findings have not, however, been confirmed by other studies, and a study in Scotland of people exposed to radium-226 indicated lower than expected numbers with prostate cancer.[60]

Links between a number of medical conditions and prostate cancer have been investigated, particularly the effects of viruses, venereal disease, vasectomy and BPH. No definitive links have been established with viruses, although a link has been suggested with the herpes virus and previous history of venereal disease.[45] Three studies have indicated a positive link with sexually-transmitted diseases, but three the opposite![42]

Small-scale studies investigated the effects on vasectomised men of having higher levels of circulating testosterone than other men. It was hypothesised that vasectomised men might be at higher risk of developing prostate cancer, but a number of studies have produced conflicting results.[11,23,42]

A large prospective study of 13,034 vasectomised men and 12,306 non-vasectomised indicated that men with a vasectomy had an age-adjusted relative risk of developing prostate cancer of 1.56 (95% CI 1.03–2.37, $p = 0.4$). In men who had had their vasectomy 20 or more years in the past, the relative risk was higher at 1.89 (95% CI 1.14–3.14, $p = 0.005$). This elevated risk persisted when adjustments were made for smoking, alcohol consumption, educational level, body mass index and geographical area of residence.[61] Although the study was well-designed, reasons for the findings have not been forthcoming and a National Institutes of Health 'meeting of experts' challenged the link between vasectomy and prostate cancer, recommending no change to existing clinical or public health practice or counselling.[62] In contrast, Japanese men are reported to have the highest rates of vasectomy, but among the lowest rates of prostate cancer. It may be that there are confounding factors present in vasectomised men which are not necessarily related to the operation.

BPH and prostate cancer are very common diseases; hence, determining whether BPH is a risk factor for prostate cancer is difficult. BPH tends to arise in the central or transitional zones of the prostate, rather than the peripheral zone. A number of studies have found a high relative risk for prostate cancer in those with BPH but the reasons for this remain unclear.[11,23,42] BPH is not generally considered to represent a premalignant state but examination of TURP tissue often reveals the presence of atypical hyperplastic lesions – including PIN and AAH.[17]

A number of other studies have suggested links between prostate cancer and a range of risk factors including, for example, cigarette smoking,[42,57,63] widowerhood,[64] lower levels of education,[47] early age at first marriage,[47] and exercise.[44] Many of these findings have not been replicated in further studies, however, and it is likely that they are of insufficient scale and contain undefined confounding factors.

Conclusion

Prostate cancer appears to be increasing throughout the world, although mortality from it remains stable. Incidence rates in Europe are approximately 55 per 100,000 per annum[7] and mortality rates between 12 and 22.6 per 100,000 person years.[26] The principal reasons for the apparent increase are the expansion of detection using increasingly simple diagnostic techniques and increasing numbers of elderly men.

The epidemiology of prostate cancer is poorly understood and documented. However, it is now generally accepted, following McNeal's work, that prostate cancer is not divided into 'latent' and 'clinical' tumours but has a very long natural history, and tumours represent particular points along the biological continuum of the disease.[16] The agents responsible for the initiation of the disease are largely unknown, although important risk factors include age, family history and possibly dietary fat.

As Whitmore[13] has said: "Only with better methods for defining the natural history of the particular tumor, more sophisticated means for anticipating life expectancy of the individual host, and good data on the effects of various treatments on the quality and quantity of survival in patients with appropriately stratified tumors will it be possible to inject more science into the extant art of treatment of the prostate cancer patient and substitute an era of cold fact for the present era of heated opinion."

Chapter 3

Diagnosis

The diagnosis of prostate cancer is made in a number of stages. 'First line' tests include DRE and serum PSA, with suspicious findings on either of these tests followed by increasingly sophisticated technologies including TRUS, and guided or random systematic biopsy. There is considerable debate within the literature concerning the most effective method of detecting early confined prostate cancer, although increasingly attention is being focused towards the development of a range of methods of utilising serum PSA levels, often in combination with DRE and TRUS. Needle biopsy then allows histological confirmation of the presence of prostate cancer.

In the sections that follow, each of the diagnostic techniques will be described and then examined in terms of their individual and combined sensitivity (probability of identifying true positives with the disease) and specificity (probability of identifying true negatives), both in a clinical and screening context.

Digital rectal examination

DRE is probably the most common diagnostic test in urological practice. It requires the insertion of a finger into the rectum to palpate the prostate gland for induration or abnormal masses. Suspected abnormalities can then be investigated further by ultrasound scan or biopsy. DRE can be carried out routinely during a clinic visit, takes only a couple of minutes, and causes relatively little discomfort. It was the principal 'first line' method for detecting the presence of prostate cancer prior to the introduction of PSA testing in the 1980s, and remains an important early and relatively uninvasive investigative test.

Characteristics of tumours detected by DRE

The aim of DRE is to detect palpable prostatic tumours. However, a proportion of the lesions that are palpable at DRE will be benign, and may be caused by conditions such as BPH, retention cysts, prostatic calculi, prostatic atrophy, fibrosis associated with prostatitis and non-specific granulomatous prostatitis. False positive rates for prostate cancer caused by DRE are as high as 40–50%[36,65–67] and, although BPH nodules that originate in the peripheral zone rarely result in abnormal findings at DRE, it is more typical for BPH originating in the transition zone to be palpable and confused with cancer.[68] The incidence of these non-malignant masses increases with age, resulting in the fall of the positive predictive value of DRE (25% in men aged under 65 years compared with 12.5% in men over the age of 65 years).[25]

Approximately 50–95% of localised prostatic tumours are palpable and could thus be detected by DRE.[32,36,65–67,69–73] The evidence for a statistically significant difference between palpable and non-palpable tumours is conflicting. Cooner and colleagues showed no difference in Gleason scores between palpable and impalpable lesions,[66] and Matthews and Fracchia found no difference between the two groups for the incidence of extracapsular disease spread in men with clinically localised prostate cancer.[74] Similarly, Devonec and colleagues found no significant difference in terms of tumour size, Gleason score or patient age between men with stage T1 and T2 palpable and non-palpable tumours.[71] A recent study by Aihara and colleagues demonstrated a significant difference in extracapsular disease.[75] They found that non-palpable T1c tumours were more likely to be confined to the prostate than palpable T2 tumours (77% versus 39%, $p < 0.001$).

Sensitivity and specificity of DRE

The sensitivity of DRE ranges from 44% to 97% in four studies that report on this factor.[25,76–78] Specificity ranges from 22% to 96% in these same studies. The positive predictive value (PPV) also varies widely, ranging from 13% to 69% in a wider number of studies, many of which evaluated other diagnostic techniques at the same time.[25,32,67,76,77,79–81] The reasons for these variable findings are probably related to the different sizes of the studies (100–6630 individuals), case selection, and variable final diagnostic criteria.

Localised prostate cancer detection by DRE alone ranges from 0.2% to 1.7% (see *Table 1*).[66,81–87] These levels are lower than those obtained using PSA, and no recent studies have assessed DRE as a single detection method. A long-term follow-up study of men with suspected prostate cancer suggests that

TABLE 1 Sensitivity, specificity and PPV of DRE alone and in conjunction with other diagnostic tests

Study	Country	No of patients	Study population	Diagnostic test	Sensitivity (%)	Specificity (%)	PPV (%)
Baran[76]	USA	666	Volunteers, aged 50 years+	DRE	89	22	35
Fogarty[79]	USA	105		DRE			19
Mettlin[25]	USA	2029	Volunteers, aged 55–70 years	DRE	58	96	20
				DRE + TRUS			32
				DRE + PSA			37
Catalona[32]	USA	6630	Volunteers, aged 50 years+	DRE			21
				DRE + PSA			69
Babaian[80]	USA	1860	Attenders at prostate detection clinic	DRE			51
				DRE + TRUS			59
				DRE + PSA			75
Drago[67]	USA	1940	Attenders at prostate detection clinic	DRE			13
				DRE + TRUS			32
Mettlin[81]	USA	2999	Volunteers, aged 55–70 years	DRE + PSA			75
Brawer[77]	USA	100	Patients undergoing radical prostatectomy for localised prostate cancer	DRE	44	71	69
				DRE + TRUS	35	74	67

the detection rate of prostate cancer by DRE declines after the first examination, falling by half after three annual examinations.[81] This is because palpable tumours are more likely to be larger and further advanced cancers.

Combining DRE with a PSA test increases the PPV by approximately 25% when the PSA level is greater than 4 ng/ml.[32,80] The American Cancer Society National Prostate Cancer Detection Project (ACS–NPCDP) is a multi-disciplinary, multicentre study in the USA to assess the feasibility of early prostate cancer detection in 2425 volunteers by DRE and PSA.[25] Findings from this study reported the PPV of a positive DRE with a PSA level below 4 ng/ml to be 19%, but when a positive DRE was combined with a PSA level greater than 4 ng/ml the PPV rose to 75.[81] Combining DRE with TRUS also enhances the PPV over that by DRE alone by 10–20%.[67,80,81] The DRE detection rate found in the ACS–NPCDP study was 1.4%.[25] For TRUS it was 1.8%.

The addition of other tests to DRE almost always raises the PPV, often considerably. DRE and PSA tests combined achieve a PPV between 37% and 75%,[25,32,80,81] and DRE plus TRUS reach a PPV of between 32% and 67%.[25,67,77,80]

Conclusion

Since the introduction of PSA testing, few studies have assessed the ability of DRE alone to detect prostate cancer. Studies which were conducted suggest that DRE is able to detect some tumours not detectable by PSA testing, but that its levels of sensitivity and specificity are inferior to PSA. There are a substantial number of additional tumours detected when DRE is used in combination with TRUS and, particularly, PSA testing over the number detected by DRE alone.[81] DRE is now unacceptable as a sole method for detecting prostate cancer. However, DRE is still an important 'first line' test, particularly for the detection of palpable tumours which may not always be detected on TRUS or by PSA testing. In addition, when DRE is used in combination with other diagnostic techniques, the rate of detection of localised prostate cancer is enhanced.

Prostate-specific antigen

The PSA blood test is quick and easy to perform and is increasingly being carried out in primary care, resulting in rising numbers of referrals to urologists. Recently, there has been much media attention devoted to prostate cancer and, particularly, its potential for screening. GPs are reporting increasing numbers of men requesting PSA tests as part of general medical examinations. The use of the PSA test in diagnosing prostate cancer has resulted in the development of what is effectively a new form of the disease – PSA-detected prostate cancer. The level of PSA is not, however, prostate cancer specific, and can be raised in a number of other circumstances. Many of the tumours detected by PSA are also small, often T1 stage, and would probably not otherwise have become apparent. PSA as the sole screening test lacks sufficient sensitivity and specificity. New methods of assessing or categorising PSA results are being developed, with the aim of improving its ability to detect early localised prostate cancer.

PSA is a 34,000 dalton serine protease produced almost exclusively by prostatic epithelium, and is present in seminal fluid, serum and urine,[88] and is thought to be involved in the liquefaction of the seminal coagulum that is formed at ejaculation. The detailed biomolecular features of PSA are described fully elsewhere.[89]

Although the name given to PSA suggests that it is related only to the prostate, recent evidence suggests that it is also expressed in minute amounts in women.[90–93] Furthermore, PSA testing is unable to distinguish between cancerous and other tissues, with elevated levels often detected in men with other 'insults' to the prostate, including BPH.[94]

PSA assays

Various assays have been developed to measure serum PSA concentrations. These include the monoclonal Hybritech Tandem-R®, Tandem-E®, IRMA-Count® and Abbott Imx® PSA assays, as well as the polyclonal Yang Pros-Check®. Small differences between the assays have been reported. Comparison of the Abbott IMx PSA assay with the Hybritech Tandem-R assay resulted in correlations between 0.97 and 0.99.[88,95] Several assays, such as the IMx, have not been calibrated at the lower levels (under 2 ng/ml).

Monoclonal and polyclonal assays both test for the same protein but rely on different measurement scales. The polyclonal assay is potentially the more sensitive,[96] but small differences have been reported between these assays.[97] It is unclear from the literature as to the degree to which any differences between assays might affect the clinical value of the PSA test.

A recent advance in PSA assay development is the enhanced reverse transcriptase-polymerase chain reaction (PCR) assay. Research is currently underway to determine if this is a more sensitive measure, but evidence is as yet inconclusive.[98]

Variation in PSA level

The normal range suggested by assay manufacturers for serum PSA levels is between 0 and 4 ng/ml, although this is subject to some debate (see below and *Table 2*). Varying proportions (25–73%) of men with no evidence of prostate cancer have serum PSA levels above the upper limits of 'normal' (defined as 0–4 ng/ml).[32,99] In addition, it is not uncommon for men with confirmed prostate cancer to have a PSA within the normal range.[33,65,100–102]

***TABLE 2** Percentage of patients with prostate cancer for three levels of PSA*

Study	No of patients with cancer	Country	Study design	Study population	Assay	Percentage with prostate cancer		
						0–4 ng/ml	4.1–10 ng/ml	> 10 ng/ml
Rommel[100]	612/2020	USA	Retrospective	Referrals for suspicious DRE, raised PSA	Hybritech Tandem R	8	30	62
Nishiya[101]	220	USA	Retrospective	Undergone radical prostatectomy	Hybritech	16	40	44
Catalona[33]	192/4962	USA	Prospective	Volunteers, aged 50 years+	Hybritech Tandem R or Tandem E	21	55	24
Mettlin[102*]	148/2999	USA	Prospective	Volunteers to prostate cancer detection program	Various	29	38	33
Viswanath[119]	56/234	UK	Retrospective	Attenders at urology clinic	ELSA–PSA2	18		82
Babaian[65]	56/124	USA	Retrospective	Patients with abnormal DRE or TRUS	Hybritech Tandem E	18	82	

** ACS NPCDP study (various PSA assays used among centres)*

Although there appear to be no diurnal variations in PSA levels,[98] several factors have been reported to affect the measured level of serum PSA, including BPH,[38,94,103] diagnostic examinations, physical exercise,[104] ejaculation,[105,106] acute and chronic prostatitis, and ductal obstruction.[107] PSA levels have also been shown to be related to the volume of the prostate and to age.[108,109]

There is a small but clinically insignificant elevation in serum PSA after DRE.[96,110] Studies have, however, been on small groups of patients, with no controls, and PSA measurements have been taken very close to examination, thus not allowing the PSA to diffuse across the physiological barriers.[96] Some findings suggest that the larger the prostate, the greater the increase in PSA after DRE.[111] Since the publication of these reports, many studies report the fact that PSA levels are determined prior to DRE.

A significant decrease in serum PSA after ejaculation has been reported in one study,[105] although it has not be confirmed by other results.[98] This potentially important factor has not been followed-up. Levanthal and colleagues reported a significant effect of exercise and activity on serum PSA in 30 men,[104] but this has yet to be confirmed in a study with adequate patient numbers.

It has also been shown that there are individual variations in PSA levels, with values decreasing over a period of a year as well as rising in men with no evidence of prostatic malignancy.[112] Pickens and colleagues measured PSA levels twice within 90 days in 307 urology patients. They reported minor changes in the mean PSA levels but more significant differences in the absolute values. One-third of the men had an increase or decrease of more than 1 ng/ml between the two measurements.[113]

PSA level appears to be significantly elevated after prostatic needle biopsy.[114] Biopsy causes anatomical disruption that leads to continuous leakage of PSA into prostatic stroma and circulation, which results in a post-traumatic inflammatory response within the prostate.[114] Following these findings Yuan and colleagues in the USA have suggested a waiting period of 4 weeks after prostatic biopsy before PSA determination can be considered valid.[114]

PSA sensitivity and specificity in prostate cancer diagnosis

When reviewing the efficacy of a diagnostic test, several parameters need to be assessed. These include sensitivity (probability of identifying true positives with the disease), specificity (probability of identifying true negatives), and positive and negative predictive values (probability that a test positive/negative individual actually has/does not have the disease)

The sensitivity, specificity, positive and negative predictive values of PSA testing are presented in *Table 3*.

Reports of PSA sensitivity range from 57–99%, with 70% being quoted at the most likely figure for screening[37,98,115–117] and specificity from 59–97%.[98,115,116] The wide variation in these values may be accounted for by several factors. There is wide variation in recruitment to studies. In the early detection studies mainly asymptomatic men have been recruited, but this is not always the case (see Powell and colleagues[118] for a study of symptomatic men). In the studies recruiting from healthy populations biases, may exist in the studies using media adverts to recruit men.[32,33] One US study recruited from a prostate cancer detection clinic set up specifically for this purpose,[80] while another study assessed men taking part in a long-term cohort study.[81] In the studies of diagnosis, all patients have been recruited from clinical settings, usually having been referred to urologists for symptoms of bladder obstruction or BPH, with a smaller number with an abnormal DRE or PSA level (*Table 4*).[115,119,120]

The gold standard test used in all the studies (diagnosis and early detection) to determine the presence of prostate cancer is the histological examination of biopsy material. As only men with suspected prostate cancer undergo biopsy, the true number of tumours present cannot accurately be determined. The criteria for biopsy vary widely between studies with criteria ranging from a single PSA measurement > 4 ng/ml to an abnormal DRE and TRUS (without PSA measurement). Thus exact comparisons between studies are difficult.

Several studies have compared sensitivity and specificity at various PSA cut-off points. As previously indicated, a proportion of men with prostate cancer have PSA levels below the manufacturers' recommended cut-off of 4.0 ng/ml. Lowering the cut-off would make the test more sensitive (more patients would be detected) but specificity would be reduced, resulting in a higher level of false-positive results.

Gillatt and colleagues in the UK assessed the ability of PSA assay to discriminate between patients with localised prostate cancer and controls.[116] The sensitivity, at a cut-off level of 4 ng/ml was 99% with a specificity of 87%. The specificity was improved to

***TABLE 3** Sensitivity, specificity, positive and negative predictive values for PSA for early detection of prostate cancer*

Study (country)	Study design†	Study population	Total no of patients	No (%) of patients with prostate cancer	Initial diagnostic tests	PSA level (ng/ml)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Powell[55] (UK)	P	Referrals to urology clinic	211	17 (8)	PSA	10	89.5	90	47	
						30		100		
Labrie1[49] (USA)	P	Randomly selected from electoral roll	1002	57 (5.6)	DRE, PSA, TRUS	4	71.4	91.1	32.5	98.2
						10	32.1	98.2	51.4	96.0
						30	17.9	99.9	90.9	95.3
Catalona[32] (USA)	P	Volunteers aged 50 years+	6630	264 (4)	DRE, PSA	> 4			31.5	
						> 4 (DRE -)			24.4	
						< 4 (DRE +)			10	
						> 4 (DRE +)			48.5	
						> 4 (DRE +, TRUS +)			54.7	
Catalona[33] (USA)	P	Volunteers aged 50 years+	4962	192 (4)	DRE, PSA	> 4	78.6	45.8	32.5	
						> 10	24	93.4	54.8	
Mettlin[81] (USA)	P	Volunteers aged 55–70 years	2999	129 (8.9)	PSA, DRE, TRUS	< 4 (DRE +)			18.8	
						> 4 (DRE +)			75	
						< 4 (DRE +, TRUS +)			27.3	
						> 4 (DRE +, TRUS +)			79.2	
Bangma[37] (Netherlands)	P	Randomly selected	812	17 (2)	DRE, PSA, TRUS	2.3	94	78		
						4	47	91		
Babaian[80] (USA)	R	Attenders at prostate detection clinic	1860	170 (9)	DRE, PSA, TRUS	> 4			59	
						> 4 (DRE+)			75	
						> 4 (TRUS+)			63	
						> 4 (DRE+, TRUS+)			79	
Clements[78] (UK)	P	Patients with positive DRE	2653							
Aziz[38] (USA)	T	Journal articles	1000	80 (52 organ confined)	PSA	4	57			
						2	(80 organ confined)			

† P, prospective; R, retrospective; T, theoretical.

97% by increasing the cut-off level to 8 ng/ml, but sensitivity was reduced to 94%.[116] The ability of PSA assay to detect men with metastatic tumours, however, was poor. At levels of 10–20 ng/ml, sensitivity was high, but specificity was so poor that many men without metastases would have a positive test result.[116]

In another UK study by Viswanath and colleagues sensitivity was reported to be lower.[119] Sensitivity for detecting cancer in symptomatic men increased, when the serum PSA cut-off level was reduced from 10 to 7 ng/ml, from 82% to 95% with a slight drop in specificity (73.5–70%).

TABLE 4 Sensitivity, specificity, positive and negative predictive values of PSA for diagnosis of prostate cancer in clinical populations

Study (country)	Study design†	Study population	Total no of patients	No (%) of patients with prostate cancer	Initial diagnostic tests	PSA level (ng/ml)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Viswanath[119] (UK)	R	Attenders at urology clinic	234	56 (24)	PSA	7 10	95 82	70 73.5	50	
Gann[115] (USA)	Nested case control	Participants in RCT of beta carotene	366 cases 1098 controls	366	PSA	4	72 (95% CI 46–90)	83 (95% CI 71–92)		
Brawer[120] (USA)	R	Attenders at urology clinics with abnormal DRE, raised PSA	218	68 (31)	PSA, DRE	2 4 10 20	93 68 24 15	23 44 92 99	34 34 57 91	88 76 74 73

† R, retrospective.

Rates of false-negative cases in prostate cancer can only be ascertained by autopsy studies of prevalence, of which there are few.[38]

In order to the increase the specificity of PSA assay in the detection of prostate cancer, several methods of measuring the antigen have been developed, including the use of age-specific reference ranges, PSA density, PSA velocity, and the measurement of free and complex PSA. In addition, a number of new assays have been developed. There is considerable debate in the literature concerning the relative abilities of these different methods and assays in the detection of early localised prostate cancer.

Age-specific reference ranges

PSA concentration has been shown to be directly related to age.[113,121–123] There are three principal reasons for this relationship. First, PSA levels are higher in men with larger prostate glands who tend to be older.[121,122] Second, as men age, the physiological barriers that keep PSA in the prostatic ductal system may also become more permeable and allow more PSA to enter the general circulation.[98,121] Third, increased PSA levels with ageing may also be influenced by prostatic ischaemia or infarction, chronic subclinical prostatitis and prostatic intraepithelial neoplasia.[98] The PSA reference range of 0.0–4.0 ng/ml does not account for these age differences or variations in prostatic volumes.[96]

The use of an age-specific reference range has the potential to make PSA level a more sensitive tumour marker for men younger than 60 years. Decreasing the upper limit of normal PSA in this population increases PSA sensitivity.[96]

In men older than 60 years, an age-specific reference range has the potential to be a more specific tumour marker, as it may reduce the number of unnecessary diagnostic procedures routinely performed in men who are unlikely to harbour life-threatening disease.[96] Data from the ACS–NPCDP longitudinal study demonstrated a specificity of 90.9% and a sensitivity of 67.3% in men with an average age of 64.5 years, when age-referenced PSA levels were analysed.[124]

Although this evidence for the use of age-specific reference ranges is quite compelling, other studies have not confirmed it. One study showed that, in men under the age of 50 years, a rise in sensitivity could only be achieved by lowering the reference range to 3.1 ng/ml.[125] This is unlikely to be clinically useful as PSA testing is rarely offered to men younger than 50 years of age. Babaian and colleagues could show no advantage of age-referenced PSA level over PSA density (PSAD) or PSA level in 581 men undergoing biopsy for prostate cancer.[126]

A prospective RCT is currently underway in 12 university centres in the USA to determine the true clinical usefulness of age-specific reference ranges compared with the standard reference range.[127]

PSA density

Serum PSA levels have been found to be related to prostate size.[107] The measurement of PSAD or PSA index (serum PSA divided by the volume of the prostate in millilitres), has been employed in an attempt to increase the specificity of PSA testing in order to distinguish between patients with BPH and those with small volume, organ-confined prostate cancer. PSAD is usually calculated prospectively based on the prostate volume determined by TRUS. In most cases, a prolate ellipsoid formula is used: $\pi/6$ (or 0.52) x (length x width x height) to determine the gland volume.[33,94,100,120,128]

The rationale for calculating PSAD is that malignant tissue produces a higher serum PSA level per gram than benign tissue.[129] PSAD > 0.15 is usually considered abnormal.[96,130,131] Reports have varied as to the increased sensitivity and specificity in the diagnosis of prostate cancer when calculating PSAD.

Several reports have indicated that PSAD offers significant advantages over PSA level alone in the evaluation of patients with benign and malignant disease.[94,103,132] The mean PSAD values for the cancer and non-cancer groups for men with a serum PSA level between 4 and 10 ng/ml have been similar in each of these studies (*Table 5*). Bretton concludes that PSAD appears to be most useful when DRE results are normal and the PSA level is greater than 4.0 ng/ml.[103]

Conversely, Catalona and colleagues and Mettlin and colleagues indicate that the sensitivity and specificity for PSAD are very close and that PSAD does not offer a particular advantage over PSA level alone.[33,124] These findings have also been reported elsewhere.[120,128,133]

The evidence suggests that the 0.15 cut-off value for PSAD may be too high to use as the basis of the determination for biopsy.[128] Catalona and colleagues reported that 47% of organ-confined, potentially curable cancers were detected by a PSA level > 4.0 ng/ml but were missed by a PSAD cut-off value of 0.15.[33]

A major difficulty with calculating PSAD is that it is unlikely that cancer volume and gland volume can be determined with complete accuracy. TRUS estimates of prostatic volume (mean 35.9 ± 1.7 cc) have been reported to differ significantly from gross pathological calculated volume (mean 45.4 ± 2.2 cc) in 100 consecutively studied men with localised prostate cancer.[134] TRUS underestimated the mean volume by 23%. Inaccurate estimations could account for some of the variation in the PSAD levels reported.

Table 5 shows that mean PSAD level is higher in men with prostate cancer than those without. However, it is doubtful whether such mean differences are clinically significant. Thus the evidence concerning PSAD as an initial diagnostic tool is equivocal. It has been suggested that PSAD may be of more use in the monitoring of disease progression, particularly in those patients with an initially low PSA level.[119]

PSA velocity

PSA velocity was introduced to increase the specificity of PSA assay. PSA velocity measures the rate of change in serum PSA over time.[129] It has been suggested that poorly differentiated cancers produce less PSA than well-differentiated cancers when equal volumes of each are

TABLE 5 *Mean PSAD values (all studies)*

Study	Country	Study design	PSA range	Mean PSAD Ca+	Mean PSAD Ca-
Mettlin[124]	USA	Prospective		0.35	0.06
Bare[128]	USA	Retrospective		0.635 ± 0.837	0.185 ± 0.260
Bretton[103]	USA	Retrospective	4.1–10	0.26 ± 0.13	0.16 ± 0.10
Seaman[94]	USA	Retrospective	4.1–10	0.285 ± 0.147	0.181 ± 0.010
Benson[131]	USA	Retrospective	4.1–10	0.297	0.188

compared and that this makes the interpretation of a single PSA test difficult.[98]

PSA velocity is determined from consecutive assessments of PSA usually at least 12 months apart. Carter and colleagues conducted a case control study and found that patients with prostate cancer had significantly greater rates of change in PSA levels than controls up to 10 years prior to diagnosis.[135] When a single PSA of 4 ng/ml or greater was used as a criterion for detection of prostate cancer, the specificity was 60%, with 40% of men with BPH being misdiagnosed as having cancer. In contrast when an average rate of change of 0.75 ng/ml or greater per year was used as the diagnostic criterion, only 10% of BPH patients were misdiagnosed, resulting in a specificity of 90%.[135]

The sensitivity of PSA velocity is reduced when a cut-off of 0.75 ng/ml per year is used in men over the age of 70 years.[136] The reasons for this are unclear but may be related to the expected increase in PSA level with ageing.[98] A prospective study by Oesterling and colleagues showed that across all age ranges, approximately 25–33% of patients without clinical evidence of cancer had more than a 20% increase in serum PSA concentration during 1 year.[137] They suggest that the upper limit of the reference range should be 0.8 ng/ml per year.[137]

In individuals, there appear to be wide variations in PSA levels from one determination to the next, which Oesterling suggests may be due to the presence of subclinical prostatitis at one determination and its absence at the next, as well as to the variation between laboratories and assays.[127]

Stamey and colleagues measured PSA levels twice within a 38 day period in 91 healthy volunteers.[138] Each of the initial PSA values were between 4 and 10 ng/ml, the clinically critical range for prostate cancer detection. From the variations reported, they concluded that to be sure that a subsequent PSA measurement is a **real** increase from the initial value, the second PSA measurement must exhibit an increase of more than 30%. Therefore, an increase from 4.0 ng/ml (normal range) to 5.2 ng/ml is within the 30% physiological variation and should not be considered significant.

There is little consensus concerning optimal spacing of PSA measurements to maximise prostate cancer detection.[136] This could have considerable cost implications if a screening programme were introduced. In the USA, Oesterling and colleagues advocate annual PSA measurements and suggest at least three PSA determinations prior to a diagnosis by velocity.[98] This has yet to be shown to the optimal application in the UK.

The results of the studies carried out in the USA to date appear promising but further research is needed, particularly in the UK, as there are a number of issues which require further investigation. For example, a prospective comparison of the various PSA indexing methods showed that PSA velocity had the highest specificity but lower sensitivity. A major disadvantage for velocity lies in the requirement for at least two PSA tests before it can be calculated. Thus direct comparison with other methods of diagnosis is difficult.[124]

Further research is also required into individual variations in PSA levels over time. If high intra-individual variation occurs naturally, then PSA velocity may be of limited use.[121]

Free and complexed PSA

PSA occurs in serum in two different molecular forms: ‘free’ and ‘complexed’ (or ‘bound’).[139,140] The predominant form of PSA is complexed with alpha$_1$–antichymotrypsin (ACT),[141] and the proportion of these complexes is higher in patients with prostate cancer.[129,140] Discrepancies in the accurate measurement of serum PSA levels may, in part, be due to the inability of standard immunoassays to detect the different forms of PSA in the same ratio.[98,141]

The amount of free PSA in the sera of men with prostate cancer is lower than in men with BPH.[142] Catalona and colleagues examined whether the measurement of free PSA would increase the specificity of the PSA test, using a Hybritech research assay specific for free PSA. Specificity was reported to be 93%, although the proportion of free PSA did not correlate with tumour stage or with patient age.[142] Age-specific reference ranges for free, complexed and total PSA have been established by Oesterling.[98]

Large differences exist among current assays in their recognition of the free uncomplexed PSA. Currently assay manufacturers calibrate their assays to free PSA.[143] Researchers are attempting to develop a standardised PSA assay based on the premise that a calibrator reflecting the ratio of PSA in the serum of patients with prostate cancer (90:10, complexed:free) will resolve most of the differences between current monoclonal and polyclonal assays.[140,143–145] There is also evidence which suggests that the concentration of measurable free PSA may fall with prolonged storage.[146]

Currently, high resolution assays are being developed to measure free and complexed PSA, which may further help to distinguish between men with BPH and those with prostate cancer.[127] Until further developments are made with the standardisation of assays to measure free and complex PSA, this method of detection has limited use in clinical practice.

The role of PSA in the early detection of prostate cancer

A combined analysis based on a review of the literature between 1988 and 1992 was undertaken to assess the role of PSA in prostate cancer detection, and a theoretical algorithm was calculated, based on 1000 hypothetical men aged 60–70 years.[38] It was assumed that 52 cases of prostate cancer should be found, and a number of different screening strategies were applied. Using a PSA cut-off level of 4 ng/ml, PSA testing would have a sensitivity of 57%, and 64% of biopsies carried out to confirm the diagnosis would be negative.[38] Reducing the cut-off value to 2 ng/ml would increase the sensitivity to 80%.[38] The authors felt that PSAD would be the best technique – resulting in a sensitivity of 69%, with only 35% of biopsies being negative.[38]

In the UK, Chadwick and colleagues screened 472 men in a large city general practice.[31] PSA and DRE were conducted on all men between the ages of 55 and 69, and TRUS was performed on those with an abnormal result. Biopsies were performed on 6% of the men and prostate cancer was detected in 1.7%. In all cases, tumours were localised to the prostate, with microscopic tumour invasion of the capsule in three cases. A raised PSA level was found for all cases of prostate cancer. However, 89% of men with a raised PSA level did not have prostate cancer, and underwent unnecessary investigations (TRUS, and in some cases biopsy).[31] Likewise, biopsies following screening have been reported elsewhere to be negative in 52% of cases in men with a PSA level < 4 ng/ml.[147]

In the USA, Catalona detected localised and advanced prostate tumours in their screening series, and concluded that they had not demonstrated an increased detection rate of early prostate cancer with PSA screening.[34] Further studies indicate that a combination of DRE and PSA assay as screening tests enhance the detection rate of organ-confined cancers.[32,35]

A nested case control study conducted on four international cohorts was conducted to assess the ability of PSA measurement to act as a screening test.[148] Serum was stored in a total of 49,261 healthy, asymptomatic men. Of these, 265 men developed prostate cancer and these were matched with 1055 controls from the same series. PSA concentrations were significantly higher in men who subsequently developed prostate cancer than in controls. In the first 3 years after blood collection the median concentration was 23 times greater in patients than in controls of the same age at the same centre. However, when the PSA levels were adjusted for age, the false-positive rate increased from 0% for men aged under 50 years, to 26% for men aged 70 years or over. The majority of men diagnosed with prostate cancer will be over the age of 65 years, and the false-positive rate from these data is too high for PSA assay to be considered as a screening tool. No outcome data were reported on the men diagnosed with prostate cancer or on the clinical stage of the tumours when they were detected.[148]

The use of PSA assay combined with DRE or TRUS results in a higher detection rate of prostate cancer than PSA measurement alone for all cancers and organ confined tumours.[32,36,65] Catalona and colleagues biopsied male volunteers on the basis of an elevated PSA level (> 4.0 ng/ml) and/or an abnormal DRE, regardless of the TRUS findings.[32] PSA assay detected significantly more tumours (82%, 216 from 264 cancers) than DRE (55%, 146 from 264, $p = 0.001$). However, 21% of the prostate cancers detected would have been missed if the decision to perform a biopsy had been based solely on the PSA value.

The sensitivity and specificity of PSA measurement used alone and in combination with other detection modalities are presented in *Tables 2* and *3*. Labrie calculated the optimal PSA cut-off value to be 3 ng/ml with a sensitivity, specificity and PPV of 81%, 85% and 24%, respectively.[149] Caution is needed in utilising standard cut-off points across races. Oesterling demonstrated that when adjusted for age, the serum PSA concentration is lower for Japanese men than for white men ($p < 0.001$) due mainly to their smaller prostate glands.[150]

The introduction of the PSA test has increased the number of tumours being detected and has led to tumours being diagnosed earlier in their natural history than previously. Moreover, these early stage T1 tumours may not develop clinically if left undetected. Evidence suggests that, even when used in combination with DRE, PSA assay lacks the degree of sensitivity and specificity required of a population screening test.

Conclusion

Level of serum PSA is claimed to be the most important and clinically useful marker in prostate cancer,[89,151,152] and has clearly had a profound impact on the early detection and monitoring of this disease.[89,98,129,130] The increase in the diagnosis of prostate cancer in recent years has, in large part, occurred following the introduction of PSA testing. Some organisations have encouraged the introduction of screening, such as the American Cancer Society and the American Urological Association, by recommending annual PSA and DRE tests for men older than 50 years,[153] and the US Food and Drug Administration by approving PSA assay for early diagnosis.[153] Other organisations, however, have recommended against screening, including the US National Cancer Institute[390] and the Canadian Urological Association. In the UK, no organisations have pronounced in favour of screening, but there has been some campaigning by particular individuals for its introduction and an increase in the *ad hoc* use of PSA testing.

While PSA assay has a number of advantages as a diagnostic test – it is quick and relatively easy to perform, and its results have been shown to be reasonably reliable and reproducible – major disadvantages remain. PSA as the sole diagnostic test lacks sensitivity and specificity. In combination with other tests, sensitivity and specificity are raised but remain relatively poor and variable. In addition, an increasing number of different assays are available which have not been standardised, and a number of different techniques are being developed in an attempt to improve its sensitivity and reliability. Currently, PSA velocity and the measurement of free and complexed PSA appear to hold the most promise but require considerable further research.

At this time, there is no evidence to encourage the widespread use of PSA testing or the introduction of population screening to detect prostate cancer.

Transrectal ultrasound imaging

TRUS is currently used in a number of ways: to estimate the size of the prostate, diagnose prostate cancer, guide needle biopsies, stage the cancers detected and to monitor disease prior to and after treatment. The evidence for the ability of TRUS in each of these roles varies. In particular, it is more accurate than DRE in the estimation of prostate size but its sensitivity and specificity in the detection of prostate cancer are poor in comparison with other measures such as PSA assay. TRUS is not normally used as a primary screening measure, but to confirm the diagnosis of prostate cancer for those with a raised PSA or lesions suspicious on DRE.

TRUS is the most commonly used imaging technique for evaluating prostate cancer. Early TRUS scans were obtained with a chair mounted 3.5 MHz probe, but contemporary equipment uses a handheld transducer with a frequency ideally between 6 and 7 MHz. This acts as an extension of the hand, and simple manoeuvring or rotation allows instantaneous multidirectional imaging.[154] A scan is usually performed with the patient lying in the left decubitus position, and this enables images to be obtained in transverse, axial, and sagittal planes, optimising evaluation of the prostate.[154,155] TRUS has recently gained increasing popularity for the evaluation of patients with prostatic disease, primarily because of the development and refinement of high-frequency endorectal transducers,[156] and with the combined use of automatic devices for biopsy.[157,158]

Determination of prostate volume by TRUS

The estimation of prostatic volume may assist in the evaluation of benign and malignant disease and can be used in the determination of appropriate therapeutic intervention.[159] In prostate cancer, prostatic volume has been shown to be a strong predictor of clinical stage and disease outcome.[160] The most commonly used methods of volume estimation by TRUS are step-section planimetry, elliptical volume and $\pi/6(\text{transverse dimension})^3$.

Planimetry gives accurate results but is time-consuming for the sonographer and uncomfortable for the patient. The ellipsoid volume calculation is a more extensively used method[158] but there is some debate concerning its accuracy.

An estimate of prostate volume by TRUS was compared to actual prostate weight after radical prostatectomy to assess the accuracy of ellipsoid volume calculation in 150 men.[159] The most commonly-used methods of volume estimation were compared for accuracy. All three methods produced similar results with correlation coefficients ranging from 0.9 to 0.94.[159]

Terris and colleagues calculated prostatic tumour volume in 110 patients by TRUS, using five different methods.[159,160] Radical prostatectomy was subsequently performed on all the men and actual cancer volume was measured. Prostatic tumours were not visualised by TRUS in 18% of cases. The step-section planimetry method correlated best with actual volume (Pearson correlation coefficient 0.84), and when the isoechoic lesions were excluded the correlation was 0.91. This method demonstrated the smallest average error (2.4 cc), but resulted in underestimation of volume in 76% of cases, particularly in larger volume tumours, with up to 17 cc underestimation. They concluded that TRUS is not accurate enough in estimating cancer volume to be used in treatment decisions,[159,160] although it is considerably more accurate than DRE.

TRUS and diagnosis of prostate cancer

Early prostate tumours typically have a non-specific appearance which require biopsy and/or histologic confirmation. TRUS can be used to detect early prostate cancer although, as it has been found to be poor at detecting tumours much below 5 x 5 mm,[156] its use as a primary diagnostic tool is limited. In addition, there is considerable difficulty in distinguishing malignant from benign tumours.

It has been reported that about 95% of prostate cancers are hypoechoic,[161] but that not all hypoechoic lesions are malignant[65,162] and as many as 50% may be benign.[65] Furthermore, there is evidence that a proportion of cancers are relatively isoechoic (undetectable) or even hyperechoic in appearance[163,164] and thus may be difficult or even impossible to detect.[165]

Inflammation or hypertrophic nodules can produce changes in the internal echoes that are similar to cancerous nodules.[166] TRUS-guided biopsy of the prostate has demonstrated that there are areas that may appear as hypoechoic within the gland, such as adenocarcinoma, atypical glandular hyperplasia, prostatic atrophy, granulomatous prostatitis, ductal dilatation and muscle around the ejaculatory ducts.[155] In a study of 160 men with stage B [T2] prostate cancer, 16% of the patients demonstrated additional hypoechoic lesions that were mistaken for malignant foci but were found to represent benign processes on pathological examination.[167] Hamper and colleagues followed a series of patients with biopsy-confirmed abnormalities identified by TRUS, and performed further TRUS examinations for up to 4 years.[79] At follow-up, 72% of the lesions had altered, either disappearing or becoming smaller, less hypoechoic, and more vague. Prostate cancer developed in only 13% of patients. Further studies have reported similar findings, including Fiorelli and colleagues who detected cancer in only 50% of those with abnormal ultrasounds.[163]

Sensitivity and specificity of TRUS

As with DRE, the value of TRUS increases considerably when it is used in conjunction with other diagnostic tests. TRUS alone results in the detection of as little as 9% of prostatic tumours, rising to 70% when used in combination with DRE.[69,76]

There is wide variation in the reported rates of sensitivity and specificity for TRUS in the diagnosis of prostate cancer. These values are presented in *Tables 6* and *7* for studies of diagnosis and early detection. Sensitivity ranges from 52% to 91% and specificity from 41% to 97%.[163,166] As with PSA, the gold standard test for determining the presence of cancer is the biopsy. The wide range of sensitivity and specificity values may be partly explained by several factors. There is a wide range of measurement differences reported between the studies. The criteria for biopsy are variable, and there are differences between the TRUS frequencies (ranging from 3 MHz to 7 MHz) used. Studies vary in the criteria used for determining an ultrasound abnormality, ranging from detailed specification of the minimum size of the lesions to broad suggestions concerning abnormality. In the majority of studies, diagnostic tests have been performed serially, with TRUS being performed only if an abnormality was detected by DRE or PSA assay.

In two studies, TRUS only was used to detect impalpable tumours in order to assess its ability to find early tumours.[161,163] The PPV of TRUS alone was lower in the studies running parallel diagnostic tests, as these series included more men who were found not to have prostate cancer. Serial testing omits those with no further abnormalities, increasing the likelihood of detecting a hypoechoic lesion.

The US ACS–NPCDP examined 2425 volunteer men and estimated the sensitivity for TRUS at 77.2% and the specificity at 89.4%.[25] The PPV was 15.2% for TRUS, with the occurrence of elevated PSA levels significantly raising the PPV.[25]

The performance of TRUS is often considered to be operator-dependent, and judgement on areas of altered echogenicity may vary between observers.[163]

No studies have reported the within- or between-observer reliability of performing TRUS or of reading ultrasound scans for prostate cancer.

TABLE 6 *Sensitivity, specificity, positive and negative predictive values for TRUS in the early detection of prostate cancer*

Study	Country	No of patients	Study population	Diagnostic test	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Clements[78]	UK	2653	Patients with positive DRE	TRUS	98	94		
Mettlin[25]	USA	2425	Volunteers, aged 55–70 years	TRUS	77	89	9	
				TRUS + DRE			32	
				TRUS + PSA			24	
Mettlin[81]			Volunteers, aged 55–70 years	TRUS + PSA (neg)			12	
				TRUS + PSA (pos)			46	
Catalona[32]	USA	6630	Volunteers, aged 50 years+	TRUS + PSA			55	
Babaian[80]	USA	436	Attenders at prostate detection clinic	TRUS			13	
				TRUS + DRE			32	
				TRUS + PSA			69	
Chodak[166]	USA	216	Volunteers with suspicious findings of prostate cancer	TRUS			36	
Drago[67]	USA	1940	Prostate cancer detection program	TRUS			13	
				TRUS + DRE			32	
				TRUS + DRE + PSA (all neg)			69	
Cooner[161]	USA	1035	Men aged 50–89 years, normal DRE	TRUS**	11	77	20	62

*** Detection of impalpable tumours only*

TABLE 7 *Sensitivity, specificity, positive and negative predictive values for TRUS in the diagnosis of localised prostate cancer*

Study	Country	No of patients	Study population	Diagnostic test	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Kelly[169]	UK	158	Symptomatic patients	TRUS	96		53	
Baran[76]	USA	314	Volunteers, aged 50 years+	TRUS	90	30	38	
Lee[69]	USA	256	Patients with hypoechoic lesions	TRUS			Stage A [T1] 22* Stage B1 [T2a,b] 42 Stage B2 [T2c] 78	
Fiorelli[163]	USA	103	Patients with bladder outlet obstruction and normal DRE	TRUS	87	66	51	92
				TRUS + PSA	92	71	64	94

** Staged by TRUS*

Technical advances in the scanning equipment used make comparisons between early and recent studies difficult. Earlier studies were conducted with 3.5 MHz scanners[166] while more recently higher frequency 7 MHz scanners have been introduced.[67,163] Furthermore, it is as yet unclear what proportion of tumours are accurately identified on TRUS due to smaller tumours being isoechoic in appearance on scan, and non-malignant lesions being identified, in some cases resulting in unnecessary biopsy.

As indicated above, the single best predictor of cancer development in men with localised disease is PSA (see above, pp.12–20). When the PSA level is greater than 4 ng/ml, the PPV of TRUS has been shown to increase from 12% (negative PSA) to 46%. When DRE is positive as well, the PPV rises to around 80%[81] or 69%.[67] This however, suggests that TRUS adds little to the predictive value of the PSA test.[79]

Colour Doppler imaging

New techniques in TRUS are being introduced, including, for example, Colour Doppler Imaging (CDI). In the early 1990s, CDI was used to detect and differentiate prostate tumours, but with limited results.[168] It has been suggested that CDI improves the specificity of TRUS imaging.[169] Rifkin and colleagues showed that blood flow in cancerous lesions of the prostate were abnormal in 86% (114 patients) of their series, in comparison with no abnormal prostatic flows in healthy controls.[168] Results of this study should, however, be interpreted with caution. No details were given of the stage of the tumours included in the study, and only ten healthy controls were studied. The consistency of CDI changes in prostate cancer was established in a prospective study by Kelly, Lees and Rickards in the UK.[169] Of the patients identified by CDI as being abnormal, 77% were found to be malignant at biopsy. The sensitivity of TRUS was 96% and the PPV 0.53. If CDI is added to TRUS in the decision to biopsy, the PPV is estimated to rise to 0.77, but to the detriment of sensitivity which would fall to 87%.[169]

Conclusion

In the UK, TRUS is routinely used as a diagnostic tool for the detection of localised prostate cancer. However, the clinical effectiveness of this modality is based predominantly on American literature, with the only UK study reviewed using CDI.

The range of reported sensitivities, specificities and PPVs (see *Tables 6* and *7*) vary widely between studies. The sensitivity of using TRUS alone ranges from 35% to 98%; specificity from 30% to 94%; and PPV from 9% to 59%. The PPV increases with the stage of the tumour detected and also increases when TRUS is combined with other diagnostic tests, such as DRE and PSA assay. The highest predictive values are achieved when TRUS, DRE and PSA assay are all performed and all are positive.

Technical advances, selection biases, observer differences in TRUS scanning, and the lack of UK studies mean that the evidence concerning the accuracy and effectiveness of TRUS for the detection and diagnosis of prostate cancer remains variable. It is generally accepted (and the evidence from the USA confirms this) that when used in conjunction with DRE and PSA measurement, TRUS will add to the detection rate of localised prostate cancer.

Needle biopsy

Needle biopsy is used to confirm the diagnosis of prostate cancer. Two main techniques are used: core biopsy and aspiration cytology. In recent years there has been a considerable increase in numbers of biopsies of the prostate in the USA, and it is likely that these increases are being mirrored in the UK. Biopsies are rising because of the increasing numbers of men found to have raised PSA levels and/or suspicious DRE results, both through the introduction of *ad hoc* screening and in general urological practice. The increasing use of TRUS has also resulted in the confirmation of greater numbers of lesions, and the introduc-tion of the thin biopsy needle has allowed a greater number of specimens to be obtained. Biopsy is an invasive test, and further research is required in order to reduce the number of tests carried out and to investigate its effects on patients' physical and psychological health.

Core biopsy

The most recent development in core biopsy apparatus is the spring loaded automatic biopsy gun (Biopty®, Bard Urological) using an 18-gauge needle with an automatic firing device, introduced in the mid-1980s. Its needle can be reliably placed into suspicious lesions in the gland using TRUS, ensuring accurate targeting. This has proved to be a much faster and accurate method than the needles previously employed which were slower to cut and tended to push and distort the prostate. Furthermore, core biopsy is reported to be reasonably comfortable for the patient.[170,171]

Aspiration cytology

Aspiration biopsies have been performed in Europe since the 1930s. The Franzen technique was first reported in the 1960s and is still widely used today. This allows the palpating finger, with the aid of a needle guide, to guide the needle to the prostatic nodule. The development of TRUS imaging has permitted the identification of non-palpable lesions. With the ultrasound probe in the rectum, slotted guides on its shaft permit positioning of the biopsy needle passed through the perineum.[172] One of the main advantages of needle aspiration is that it can be performed without anaesthetic as an out-patient procedure. In addition, the fine calibre of the needle allows small nodules to be accurately aspirated, and multiple samples can be taken during the procedure.

However, the ability of this method to detect early cancers has yet to be adequately proved.

Agatstein and colleagues[173] compared the findings of aspiration biopsies prior to prostatectomy in men with clinically benign digital examinations. They reported a 14.75 incidence of stage A1 [T1, T2] and 3.9% incidence of stage A2 [T2, T3] prostate cancer. There were no false positive aspirations in any patient with BPH. When adequate diagnostic material was obtained, fine needle aspiration detected all cases of stage A2 [T2, T3] disease but no cases of stage A1 [T1, T2] disease. Thus, in this study aspiration cytology proved better able to detect stage A2 [T2, T3] prostate cancer than DRE alone.

Tumour detection

A number of studies of men with suspected prostate cancer have compared the performance of aspiration and core biopsy. The results of the major studies are presented in *Table 8*. Narayan and colleagues compared the ability of aspiration and core biopsy to detect prostate cancer in 121 consecutive patients.[174] No patients with negative aspiration biopsies had positive core biopsies and the number of false negative results was fewer with the aspiration technique. However, neither biopsy technique was able to identify stage A [T1] carcinomas, which were subsequently identified in patients undergoing TURP for BPH.[174] Radge and colleagues detected 102 carcinomas in 292 consecutive patients.[175] Forty-two were positive by both techniques, 11 were positive by aspiration cytology alone, and 49 by core biopsy alone. The sensitivities reported for each method were 89% for core biopsy and 51% for aspiration cytology and the difference between the two was significant ($p < 0.001$). Of the cancers detected, 35 were not palpable and were identified by ultrasound.[175]

Waisman and colleagues found the sensitivity of aspiration cytology (95%) to be higher than for core biopsy (90%) when omitting inconclusive biopsy results, in their study of 99 men.[176] Their study was flawed by including 38 patients with a prior confirmed diagnosis of adenocarcinoma of the prostate. However, high false-negative findings have been reported on aspiration cytology performed on a screening population.[177]

Evidence from the literature suggests that when the tumour is palpable, aspiration cytology has been demonstrated to be superior to core biopsy techniques. It is less clear, however, how sensitive aspiration cytology is in relation to non-palpable tumours. Furthermore, the majority of the literature relates to studies that have been carried out in the USA, and thus conclusions must be tentative in relation to the performance of prostate biopsies in the UK.

The utility of aspiration biopsy to identify incidental prostatic tumours in men undergoing TURP has been assessed by Honig and colleagues.[178] Fine needle aspiration biopsies were conducted on 100 consecutive patients immediately prior to TURP. Specimens from both procedures were analysed for evidence of cancer. A total of 14 patients had disease diagnosed as adenocarcinoma, five diagnosed by histological examination alone, four by cytological examination alone and one by both techniques. As each procedure samples different portions of the prostate gland, the concomitant use of aspiration cytology and TURP increased the incidence of adenocarcinoma from 10% to

TABLE 8 *Aspiration and core biopsy – comparison of sensitivity, specificity and PPV*

Study	Study type	Subjects	Palpable/ non-palpable	Aspiration cytology			Core biopsy		
				Sensitivity	**Specificity**	**PPV**	**Sensitivity**	**Specificity**	**PPV**
Radge[175]	Retrospective	292 patients with suspected prostate cancer	Palpable and non-palpable	51%			89%		
Polito[182]	Retrospective	605 patients with suspected prostate cancer	Palpable only	93%	98%				
Waisman[176]	Retrospective	99 patients (38 with prior diagnosis of prostate cancer)	Palpable only	95%			90%		
Liung[180]	Retrospective	103 patients		95%	97%		74%	100%	

14%.[178] However, the costs and benefits of detecting incidental carcinoma have yet to be established.

The high numbers of false negative results of aspiration biopsy when taken at random prior to TURP, have also been reported elsewhere.[177,179] Only seven out of 49 patients with prostate cancer, diagnosed by histological examination of TURP specimens, could be found with aspiration cytology and a further seven had suspect findings.[177] Liung and colleagues reported a lower false negative rate (3 from 41 'benign' cases); however, there were no details of their study population.[180]

These studies suggest a poor sensitivity for aspiration cytology. Furthermore, the value of actively trying to identify prostatic tumours in TURP patients is questionable. It is unclear from the reported studies whether treatment would alter as a result of the detection of these tumours, as all the men were already undergoing TURP.

Sensitivity and specificity of core biopsy and aspiration cytology are presented in *Table 8*. Differences between the values may be due to differences in the methods of sample collection and variability in the ability of the cytopathologist to report on the samples.

Interpretation of biopsy results

There are two key issues which relate to the interpretation of the results of diagnostic studies by biopsy. The first is the adequacy of the specimen obtained and the second is the accuracy of the interpretation of the specimen.

The frequency of obtaining a specimen adequate for diagnosis is an important characteristic of any biopsy technique.[172] Cytological specimens are subject to inadequacy not only due to guidance and quantity problems, but also due to artefacts of technique, such as drying.[172]

The rate of inadequate sampling, although often unreported, ranges from 0.2% to 33% for aspiration biopsy.[171,173–175,177,179,181–183] Reported rates of inadequate core biopsy specimens range from 0% to 11%.[174,175] Carter and colleagues reported that of the 94 prostatic aspirations that could be given a definite cytological diagnosis there was eventual histological correlation in 85 (90.4%).[183] A false negative rate for fine needle aspiration was reported as 2.7%, and the rate for core biopsy, 5.3%. Higher levels of false-negative results have been reported (27.9%) when performed by trainees with varying degrees of experience and skill.[179]

Effectiveness of diagnosis by biopsy

Digitally- and TRUS-guided biopsies

Biopsies may be digitally- or TRUS-guided. Several studies have compared the use of digitally-guided and TRUS-guided biopsies in men with palpable lesions.[184–186] In three studies, TRUS-guided biopsy increased the number of tumours detected over those detected by digitally-guided biopsy alone (four,[186] eight[184] and 44[185] additional tumours). In the study by Lippman and colleagues each of the additionally detected tumours came from the area of palpable abnormality previously reported as benign.[186] Several other studies have been conducted comparing the two methods, but the numbers of patients in these series are too small to include in this review.

Random/systematic biopsy

As reported earlier (see Chapter 3, pp.21–23), up to 40% of prostate cancers are isoechoic and are often multifocal. Published reports differ about whether TRUS-guided biopsies should be directed exclusively at hypoechoic lesions that are suggestive of carcinoma or if random biopsies of lobes that appear normal should also be included.[187] The key issue with random/systematic biopsies is the ability of this procedure to detect cancers of clinical significance (less than 0.5 cc volume), but which may be missed by TRUS- guided biopsy.

Random biopsy has been reported to have detected between 14% and 94% of the total number of cancers detected, when used in addition to TRUS-directed biopsy (*Table 9*).[173,188–191] The wide detection range can be attributed to the fact that these studies are not directly comparable. A lower detection rate by random biopsy alone was found in patients who all had suspicious lesions on TRUS[191] because the exact area of tumour was not identified when random biopsies were taken. Higher detection rates were reported in studies which included clinical stage B or C [T2, T3] patients with palpable lesions and who had not previously been assessed by TRUS.[189,190] In addition, it is difficult to assess in some studies the degree to which tumours would have been detected by random biopsy alone, as guided biopsy was performed first, with random cores being taken from the remaining lobes.[190,192]

Slonim and colleagues assessed 570 men with suspected prostate cancer, using random and guided TRUS biopsies.[187] They found that patients with a hypoechoic lesion had a significantly increased likelihood of having cancer compared with those who had no hypoechoic lesion ($p < 0.0001$). However, carcinoma was detected with directed biopsy in only 145 of 202 (72%) of the patients with

TABLE 9 Number (and percentage) of tumours detected by directed and/or random biopsy

Study	No of patients	Number (%) positive for cancer	Tumours (%) detected by directed biopsy	Tumours (%) detected by random biopsy
Hodge[189]	136 (DRE abnormal)	83 (61)	3 (6) Additional to random	80 (94)
Vallencien[192]	100	14 (14)	2 (14)	12 (86)
Dyke[191]	164 (114 DRE abnormal; 14 TURP-detected; other clinically detected)	71 (43)	56 (79)	5 (7) Additional to directed [+ 10 (14) detected by both methods combined]
Olson[190]	141 (DRE or PSA detected)	40 (28)	27 (68)	13 (32) Additional to directed
Slonim[187]	570 (DRE, PSA and other clinical abnormalities)	202 (35)	145 (72)	57 (28) Additional to directed
Garber[188]	669 (DRE, PSA or both abnormal)	233 (35)	169 (73)*	56% in TRUS-normal glands

* *Combined biopsy methods*

cancer.[187] In another group of 153 patients with unilateral palpable lesions, TRUS-guided needle biopsies were carried out on both lobes of the prostate.[193] Sixty-five of the patients were found to have bilateral tumours, 37 of which were also unidentified by TRUS in the contralateral lobe. Those patients with tumour biopsied from both lobes had a significantly increased risk of capsular penetration of tumour into the periprostatic fat (72% versus 28%, $p = 0.025$). It would appear that patients with unilateral palpable cancer often have bilateral disease which is often not evident even on TRUS, but which can be detected by needle biopsy.

Terris and colleagues performed systematic biopsies on 816 men who were referred with an abnormal DRE or raised PSA level.[194] TRUS-guided biopsies were performed on six sites in each patient. Prostate cancer was detected in 442 men (54%) and, of these, 60 (14%) had cancer detected as a single minute focus of 3 mm or less in only one site, which may not have required treatment. They report an overall risk of detecting an insignificant cancer as 4% with systematic biopsies.[194]

Garber and colleagues compared TRUS findings with biopsy results in 669 men with suspected cancer, performing random biopsies on six sites, guiding the needle to areas of abnormality when necessary.[188] Of the 669 men, 60% had an abnormal TRUS and, of these, 42% were found to have malignancies detected by ultrasound guided biopsy. A further 64 (24%) malignant lesions were detected in those with normal TRUS by random biopsy. They reported that an additional 8% of cancers were detected because of the random biopsies.[188]

In summary, the evidence suggests that random biopsy identifies a significant number of additional tumours that would have been missed by guided biopsy alone. The proportion of additional tumours detected varies between studies and, in some cases, the tumours detected are extremely small.

The key issue is whether any additional tumours detected by random biopsy are clinically significant. The number of positive random biopsy specimens obtained from a patient may be a good prognostic indicator of pathologic classification and tumour volume. Peller and colleagues found that the number of positive sextant biopsies correlated with preoperative PSA level, tumour volume, pathological stage, Gleason score, seminal vesicle involvement and capsular penetration.[195]

It is difficult to compare studies examining diagnostic rates with random and guided biopsies because of marked differences in inclusion criteria for the studies. In a group of 164 men with a solitary hypoechoic prostatic nodule at entry, Gleason scores were reported to be significantly higher ($p < 0.05$) in men with hypoechoic lesions (mean 6.3) than in men whose cancer was detected in isoechoic random sites (mean 4.9). Gleason scores in patients with positive random biopsies alone were the lowest (mean 3.8).[191] Hammerer and col-

TABLE 10 *Post core biopsy complications*

Study (year)	No of cases	Biopsy type	Prophylactic antibiotics administered	Morbidity
Carter (1986)[183]	110	Core + aspiration	Yes (46)	Ileus (1)) Clot retention/hospital admission (1)) prophylaxis Febrile episode (1)) received
Ragde (1988)[175]	292	Core + aspiration	No	High fever and presumed septicaemia (1)
Narayan (1989)[174]	203	Core + aspiration	Yes	Haematuria requiring clot evacuation (3) Blood transfusion (1)
Hodge (1989)[189]	136	Core	Yes	Unspecified
Torp-Pederson (1989)[254]	149	Core	Yes (34) No (104)	Blood in urine (51) Blood in stool (13) Blood in ejaculate (7) Transient fever (1)) did not receive Fever requiring antibiotics (1)) prophylaxis
Hodge (1989)[355]	251	Core	Yes	Chills/fever requiring hospitalisation (1) Rectal mucosal bleeding (3) Urinary retention (1)
Dyke (1990)[191]	164	Core	Yes	Mild fever (3.6%)
Vallencien (1991)[192]	100	Core	Yes	Fever (7), hospital admissions (2) Myocardial infarction (1)
Narayan (1991)[356]	94	Core + aspiration	Yes	Prolonged haematuria (2) Bladder irrigation (1)
Cooper (1991)[184]	66	Core	Yes	Unspecified
Rifkin (1991)[185]	112	Core	Yes	No complications
Coplen (1991)[357]	73	Core	Yes	Urosepsis/hospital admission (1)
Renfer (1991)[358]	100	Core + aspiration	Yes	Gross haematuria (2) Mild rectal bleeding (2)
Allen (1991)[171]	182	Core + aspiration	No	Unspecified
Waisman (1991)[176]	99	Core + aspiration	Yes	Fever (4), hospital admission (2)
Terris (1992)[194]	816	Core	Yes	Unspecified
Daniels (1992)[193]	153	Core	Yes	Unspecified
Slonim (1993)[187]	570	Core	Yes	No major or significant minor complications
Olson (1994)[190]	141	Core	Yes	Unspecified
Hammerer (1994)[170]	651	Core	Yes	Haemospermia (35) Haematuria (88) Rectal bleeding (14) Infection (5)
Peller (1994)[195]	102	Core	Unspecified	Unspecified

leagues in their study of random and guided core biopsies, assessed a subset of 14 patients in whom only one of six core biopsies were positive for prostatic cancer.[170] All 14 men underwent radical prostatectomy and tumour sizes in the specimens were estimated. All of the tumours were more than 10 mm in diameter and, in six, the tumour was multifocal or showed capsular infiltration.[170] Thus the cancers detected by random biopsy in this study were clinically significant. The number of positive random biopsies has been shown to be an important prognostic indicator.

Evidence concerning the stage of tumours detected by random biopsy is, however, inconclusive. Peller found that stage increased with the number of positive sextant biopsies,[195] Hammerer found that 50% of the tumours detected were stage B [T2] (50% were stage A[T1]),[170] and Dyke reported that the random biopsy did not result in significant alteration of clinical staging.[191] Again, tentative conclusions must be drawn in generalising this evidence to the UK, as no studies have been reported from the UK, and the majority of the literature has been published in the USA.

Complications of prostatic biopsy

Needle track seeding

Implantation of tumour along a needle biopsy track is a recognised potential complication of this procedure. Implantation or seeding is infrequent but more likely to occur with transperineal core biopsy than the transrectal route.[172,196] Few recent series have presented data on the occurrence of tumour tracking. Bastacky and colleagues reported on a series of 350 patients undergoing radical prostatectomy on whom a prior core biopsy had been performed.[197] Seven cases (2%) of needle biopsy tracking were identified, three in which the only area of capsular penetration was limited to the needle track. Histological grading of the tracking component consistently correlated with that of the tumour within the gland (Gleason score 5 to 7 in six cases; Gleason score 9 in one case). Moul and colleagues report an incidence of five cases of perineal seeding from 2107 patients undergoing core biopsies at one institution over an 11-year period.[198] All patients had at least clinical stage C [T3] disease and all had received definitive primary radiotherapy. Seeding occurred in four cases prior to hormonal therapy, which has previously been postulated as a precipitating factor in seeding.[198]

While the overall risk of this complication is low, it is not insignificant.

Other complications

After combined aspiration and core biopsy, most patients report mild transient haematuria,[175] although some have experienced more severe complications. Post-biopsy complications are reported in *Table 10* for core and aspiration biopsies. In most cases prophylactic antibiotics are administered to patients undergoing biopsy. It is not possible to assess the level of complications if antibiotics were not administered. Carter and colleagues administered perioperative antibiotics to 41% of their patients undergoing biopsy.[183] Three of the patients receiving anti-biotics experienced complications (see *Table 10*). There were no complications in the patients who did not receive antibiotics. No reasons were indicated for giving some patients prophylactic treatment, but are likely to be related to clinician preference and perceived increased risk of infection.

Conclusion

With recent technical advances of core biopsy instruments, this method has become as quick and easy to perform and more tolerable for patients as aspiration cytology, and now appears to be used more often. Post-biopsy complications, while still a risk, are relatively rare with the use of prophylactic antibiotics. The rate of complications ranges from 0.7% to 13.5% in patients given antibiotics, and from 0.3% to 34% in patients given no antibiotics (see *Table 10*). A majority of the reported studies have been carried out in the USA. There may be differences in the way in which biopsies are carried out in the UK, in terms of the techniques used and the choice of patient biopsied, and so these results should be interpreted with caution.

There are a number of further reasons why results from biopsy studies should be scrutinised carefully. Studies vary in their inclusion criteria. In some, men undergoing TURP are included, while in others, men suspected of having prostate cancer on the basis of palpable or sonographic lesions are included. There may also be lack of comparability between biopsy methods because regardless of the technique used, the greater the number of times the prostate is biopsied the greater the likelihood of detecting it.[186] Further, biopsy specimens vary in the way in which cores are prepared and submitted for processing in the laboratory.[199,200]

Staging from core biopsy specimens also has a number of problems. First, the angle of the needle as it enters the prostate through the peripheral zone will enable the length of the tumour to be measured from the core sample, but an accurate measurement of the diameter is more difficult to assess as this may not be sampled, and core tissue can undergo distortion during handling.[191] Second, different patterns of tumour involvement may require different measurement techniques. Core samples may contain single sections of tumour, several sections from a single tumour or may be interspersed with normal and abnormal tissue. Details of tumour measurement are often not specified in studies and so comparisons are again made more difficult.

Prostate cancer can be detected by biopsy either in areas identified as suspicious by DRE or TRUS, or by systematic sampling of apparently normal prostates. Random biopsies offer the potential of discovering tumours which have escaped detection by other means – although the benefit of this is questionable.[194] They are also costly in terms of performance and analysis, and result in some patient discomfort.[188]

Evidence suggests a combination of random biopsies with directed biopsy of hypoechoic lesions (when identified) to be the method which detects the greatest numbers of tumours, but this inevitably results in a large number of biopsies being carried out on patients who do not actually have prostate cancer. Biopsy does not have a role in first line screening but remains important for histological confirmation of the presence of organ-confined prostate cancer.

Chapter 4

Staging systems and methods

The ability to stage prostate cancer accurately is of vital importance as a guide to prognosis and forms the basis upon which the initial management of patients is decided. Several diagnostic tools are available for clinical staging, including DRE, TRUS and PSA assay. Following initial clinical staging, computed tomography (CT), magnetic resonance imaging (MRI) and radionuclide bone scans are imaging techniques used as a more accurate assessment of clinical stage. Tumour differentiation is carried out following biopsy or surgery. Surgical staging is carried out by performing a lymphadenectomy, usually done prior to radical prostatectomy. Histological evidence provides the 'gold standard' method of staging, although clearly this is not possible for all patients.

As yet there is no consensus among clinicians as to the most accurate and cost-effective clinical staging modality, and the situation is complicated by the number of different staging systems which overlap but are not directly comparable. In addition, technological developments are occurring and so methods of staging are changing rapidly, often without adequate evaluation.

Staging systems

Two major staging systems are used: the ABCD (modified Whitmore-Jewett) system, popular in the USA, and the TNM (tumour-node-metastases) classification which is widely accepted in Europe. The fourth revision of the TNM classification was introduced in 1987.[201] The results of a consensus seminar on the TNM classification were published in 1992, providing a unified and uniform TNM system.[202] A partial summary of the TNM system is presented in *Table 11,* focusing on non-metastasised disease.

The TNM classification serves both clinical and pathological staging.[202] In clinical staging, primary tumour assessment includes DRE, PSA testing and

TABLE 11 *The TNM classification (compiled from information in Schroder* et al[202] *that relates primarily to localised disease; (classifications of N and M relate to metastases)*

Classification	Description
	Incidental prostate cancer
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
T1	Clinically unapparent tumour, not palpable nor visible by imaging
T1a	Tumour an incidental histological finding in 5% or less of tissue resected
T1b	Tumour an incidental histological finding in more than 5% of tissue resected
T1c	Tumour identified by needle biopsy (e.g. because of elevated serum PSA level)
	Palpable or visible carcinoma confined to the prostate
T2*	Tumour confined within the prostate
T2a	Tumour involves half of a lobe or less
T2b	Tumour involves more than half a lobe but not both lobes
T2c	Tumour involves both lobes
	Locally extensive prostate cancer
T3†	Tumour extends through the prostate capsule
T3a	Unilateral extracapsular extension
T3b	Bilateral extracapsular extension
T3c	Tumour invades seminal vesicle(s)
	Locally extensive tumours with fixation or invasion into neighbouring organs
T4	Tumour is fixed or invades adjacent structures other than seminal vesicles
T4a	Tumour invades bladder neck and/or external sphincter and/or rectum
T4b	Tumour invades levator muscles and/or is fixed to pelvic wall

** Tumour found in one or both lobes by needle biopsy, but not palpable or visible by imaging, is classified as T1c.*
† Invasion into the prostatic apex or into (but not beyond) the prostatic capsule is not classified as T3 but as T2.

***TABLE 12** Comparison of TNM[202] and Whitmore-Jewett[13,203] classifications for staging prostate cancer*

TNM classification	Whitmore-Jewett
T1	A
T1,T2	A1
T2,T3	A2
T2	B
T2a,T2b	B1
T2c	B2
T3	C
T3a,T3b	C1
T3c	C2
M and N	D

imaging by TRUS. In pathological staging, histological examination of a resected specimen is required, with pelvic node dissection where appropriate.

A principal weakness of the ABCD system is its inability to characterise regional lymph nodes (N+) or distant metastases (M+) relative to the category of the lesion. All N+ or M+ lesions are categorised as stage D. *Table 12* gives a comparison between the TNM classification and the Whitmore-Jewitt system.[203] There are a number of overlaps, caused by the different bases of these systems.

The TNM system is the major method of classifying staging in use currently, although a considerable part of the literature contains either an early version of the system or other methods.

For the purposes of this review, the latest version of the TNM system has been adopted.[202] Throughout the review, the systems used by individual authors have been used but, wherever possible, the equivalent TNM classification (taken from *Table 12*) has been added in square brackets to aid the reader.

Methods for clinical staging

DRE

DRE plays a crucial role in identifying T1 tumours, and also in the differentiation between T1, T2, T3 and T4 tumours. It is also the most commonly used initial clinical method of diagnosing and staging prostate cancer. There are, however, considerable concerns about the accuracy and reproducibility of DRE, particularly with regard to tumours where the capsular breach may occur away from the examining finger.[204] (See also Chapter 3, pp.11–12).

PSA

As indicated elsewhere, the increasing use of PSA testing has led to a rise in the diagnosis of incidentally found prostate cancers, particularly T1c tumours. PSA testing cannot, however, classify the extent of the primary tumour, and this has to be confirmed by DRE and/or imaging.[202] In addition, the presence of extracapsular extension is missed in 25–38% of cases by the use of PSA testing alone.[205,206] The ability of the PSA assay to predict bone metastases has been reported to be higher than for extracapsular extension. When PSA testing is combined with Gleason score, for example, the prediction of metastases is enhanced.[207]

TRUS

TRUS is used in the clinical staging of prostate cancer, but some variability in the appearance of prostatic tumours on ultrasound has been noted, particularly for tumours within the transition zone.[154,164] (see Chapter 3, pp.20–23). The sensitivity of TRUS in detecting seminal vesicle involvement has been reported to be 62% with a specificity of 76%.[208]

TRUS can be used to determine tumour volume, which has been shown to correlate with lymph node metastases.[209] However, the reliability of tumour volume determination by TRUS has been questioned.[210] The smallest tumour visualised by TRUS is about 4.5 mm in diameter when measured on the surgical specimen, but as a staging technique TRUS has been shown to underestimate the size of the tumour by up to almost 5 mm.[211] TRUS is more accurate than DRE in staging prostate cancer by detecting capsular breaches and assessing apical or seminal vesicle involvement.[155] Tumours detected on TRUS tend to be larger, well-differentiated and palpable, suggesting that TRUS tends to detect and stage tumours that are clinically important.[211]

MRI

MRI offers images of the prostate in three planes, enabling better evaluation of lesions. Areas not well visualised in one plane can be evaluated in two others, and suspicious areas in one plane can be confirmed in another.[203] Early results of MRI in the evaluation of prostate cancer were promising but, as more experience has been gained, more conflicting reports have been published.[208,212] Rapidly-evolving technology can mean that, by the time an evaluation is completed using adequ-ate patient numbers, the specific techniques and equipment used may no longer be ‘state of the art’. Further, many of the studies involve comparisons between prospective and retrospective series, involve biases such as the inclusion of selected versus consecutive patients, include only small numbers of patients, and use variable methods of pathological staging.[213] Another difficulty with comparing the existing studies using MRI is that different parameters and planes of imaging have been used.

Several studies have been published which assess the sensitivity and specificity of MRI as a staging technique.[212,214] Sensitivity and specificity for MRI range from 35% to 75% and from 81% to 88%, respectively, and PPV and NPV range from 58% to 83% and from 62% to 82%, respectively. The range is accounted for by the increased accuracy of this modality when staging T2 tumours than T1 tumours which are more difficult to stage accurately.[212] Differences in sensitivity are also noted between tumours detected at the posterior or the anterior of the gland, with those detected posteriorly having greater sensitivity (85% versus 15%).[215] MRI is also limited by the high false-positive rate in the depiction of non-palpable tumours.[215] False-negative results can occur in up to 50% of cases assessed for positive lymph nodes, and 55% of those assessed for seminal vesicle invasion.[208]

There has been great debate regarding the ability of MRI to differentiate local disease from unconfined disease.[203] It has been suggested that poorly differentiated tumours are more difficult to image with MRI, in contrast to well- or moderately-differentiated tumours which have clearly defined margins.[216] Bezzi and colleagues in the USA reported a sensitivity of 72%, specificity of 84% and accuracy of 78% in differentiating localised from extracapsular disease by MRI.[217] The MRI sensitivity for the detection of lymph node metastases was 69%, with a specificity of 95% and an accuracy of 88%.[217]

Several recent advances hold some promise in relation to staging of prostatic cancer. These are the use of endorectal surface coils and new pulse sequences.[218] Endorectal surface coils yield higher resolution images of the prostate than previous techniques due to the balloon-mounted coil being inserted into the rectum and inflated. In this way, the coil is placed closer to the prostate gland than external coils placed outside the rectum.[203] However, the numbers of patients involved in the studies of these new techniques are small.[218] Although new techniques often appear to promise much for the future, there is still some caution concerning the use of body coil MRI to predict early capsular breach, both in the UK and USA.[219–221]

Computed tomography

In the 1980s, CT replaced lymphography as the initial method of lymphatic imaging in patients with prostate cancer.[222] CT can accurately display gland shape and size, but is unable to stage local involvement.[203,223] The current role of CT is to delineate the extent of tumour spread and identify local pelvic metastases.[224]

In a UK series of 104 consecutive patients with clinically-localised prostate cancer staged by CT, 13% of patients were found to have lymph node positive disease.[222] Comparison with pathological data suggested that lymph node enlargement was associated with less well-differentiated tumours.[222] CT scanning has been associated with a relatively high yield of false-positive results.[208] Sensitivity and specificity are approximately 55% and 73%, respectively and PPV and NPV are 61% and 68%, respectively.[212]

A comparison with MRI shows MRI to be the more specific modality. It is more sensitive in the staging of T2 tumours but less sensitive in the staging of T1 tumours.[216,219] Upstaging by CT has been estimated to occur in approximately 40–50% of cases.[222,225] However, evidence suggests that prostate cancer still remains significantly understaged with pre-operative CT scans.[225] Several studies have suggested and tested refined procedures for CT scanning, but only on a small number of patients.[223]

Radionuclide bone scans

The radionuclide bone scan (also termed scintigraphy) is the primary method for checking for metastases to bone.[226] It is a standard staging method in the USA, and is used to some degree in the UK. In prostate cancer, bone is the most common site of distant metastases. Although the bone scan is accurate at detecting the presence of bony metastatic disease,[227] it is too costly and time consuming to be performed routinely in the UK. Oesterling recently suggested that for patients with a PSA below 20 ng/ml and no skeletal symptoms, staging by radionuclide bone scan does not appear necessary.[228] This has been supported by other reports.[206] These findings were, however, questioned in a later study in which 2.6% of patients with a PSA level of 20 ng/ml or less were, nevertheless, found to have a positive bone scan, compared with 0.6% in the Oesterling study.[227] More highly selected patients in Oesterling's study would appear to account for the differences between the results of these two studies. However, among asymptomatic, untreated men with prostate cancer and a serum PSA level of 10 ng/ml or less, a staging bone scan does not appear necessary.[227]

Few studies evaluating the use of bone scans have been conducted in the UK. O'Donoghue and colleagues followed a series of patients with newly diagnosed prostate cancer for a minimum of 12 months.[229] All patients had isotope bone scans performed at presentation and then at yearly intervals. The proportion of patients with a raised PSA level increased with clinical stage as did the proportion with bone metastases. Some 6% of patients with clinically-localised tumours (stages A and B [T1, T2]) were found to have bone metastases, although it is not clear how many of these had developed by diagnosis and how many were detected during follow-up. PSA level was found to be an excellent marker of bone metastases, with a PPV of 95.7% at presentation and 100% at follow-up.[229]

As with all the radiographic staging techniques, the results are only as accurate as the individuals reading the scans. Little work has been published assessing the intra- and inter-individual accuracy in using these techniques in staging prostate cancer, although training and experience do appear to be important factors.

Pelvic lymph node evaluation

Evaluation of the pelvic lymph nodes for metastases is important in prostate cancer as patients with positive lymph nodes have a markedly worse prognosis compared with those with negative lymph nodes. Surgical staging of the lymph nodes has been the gold standard, performed prior to radical prostatectomy, and provides staging information that cannot be obtained by any other method.[230] However, the risks and costs associated with routine staging pelvic lymphadenectomy have raised questions on the need for this procedure.[207] More recently, laparoscopic lymph node dissection has become more widely used.[231] No studies have compared these two techniques.

Gleason histological grading

Biopsy specimens are graded histologically based on the architectural differentiation of the tumour cells,[232] and this has been reported to be a good, although imperfect, method of predicting lymph node metastases.

The predominant histological system is the Gleason grading system in which sections of tumour are graded from 1 (least aggressive) to 5 (most aggressive). The two highest grades from each tumour are added to give a score ranging from 2 to 10. Tumours with a score of less than 7 tend to have a good prognosis, while those with a score of 7 and above tend to have a poorer prognosis.[11]

Gleason score is associated with more aggressive tumours and several studies have shown Gleason score to be the best predictor of progression.[233] Preoperative Gleason score correlates with tumour volume and extracapsular extension,[209] but not with positive margins.[234] The relationship between Gleason score and tumour grade has been found to be highly significant ($p < 0.0001$), but the correlation between the two is relatively poor ($r = 0.25$).[235] Disease progression is more likely to occur in men with tumours of higher grade than those with a lower grade. In a series of 504 patients undergoing radical prostatectomy in the USA, 13% of those with Gleason scores of less than 7 had progressed at 5 years, compared with 59% of those with a Gleason score of 7 or more ($p < 0.0001$).[233]

A study comparing the reproducibility and accuracy of four histological grading systems (MD Anderson Hospital, Mostofi, Bocking and Gleason systems) reported the Gleason system to be the least reproducible,[236] although no details were included on the content of the other grading systems for comparison.

DNA ploidy

There has been a growing interest in DNA ploidy of localised prostate cancer. Studies have shown that cells of prostate cancers which are clinically or pathologically confined within the prostate capsule are DNA diploid (or normal) in approximately 70–80% of cases.[210,237] (For further details, see Leiber.[238]) Ross and colleagues found no statistical association between Gleason grades for biopsy and corresponding prostatectomy specimens from a series of 89 patients with localised prostate cancer.[239] There was, however, a high correlation of ploidy status between the biopsy and surgical specimens ($p < 0.0001$).[239] High correlations have also been shown between non-diploid tumours and disease progression.[240] DNA ploidy also seems to correlate with the aggressiveness of tumours.[11]

Somewhat conflicting data show that ploidy status alone cannot accurately predict disease progression. In a retrospective study of 186 post-prostatectomy patients, aneuploid tumours (usually associated with poor prognosis) were identified in 16%. Of these, 47% were still alive at 10 years, and 30% were apparently disease-free.[237] Another study showed Gleason score to be a better predictor of progression than ploidy. (Gleason score predicted progression at $p < 0.0001$).[241]

Conclusion

The ability to stage and grade prostate cancer accurately is of vital importance for prognosis and the choice of suitable treatment options. The staging and grading modalities currently available do not, however, always provide an accurate evaluation. Understaging occurs in 40–65% of men with clinically localised disease,[212,225,242] with rates of 63% for extracapsular extension, 23% for positive surgical margins and 8% for positive lymph nodes.[243] Particular difficulties have been recognised in identifying stage A [T1] disease.[244] In several series of men with clinical stage A [T1] disease undergoing radical prostatectomy, pathological analysis shows between 10% and 30% may have extracapsular disease[210,243]

There are methodological and technical problems with many of the studies performed on clinical staging. Many of the reported staging studies are carried out on series of men with clinically localised disease, who have elected to undergo radical prostatectomy,[207,225,243,245,246] to allow comparison of clinical stage with pathological stage on examination of the prostate. There may be biases inherent in these study groups, for example, men undergoing surgery are more likely to be younger and fitter than those undergoing conservative management.

There may also be pathological differences which can bias the results of staging studies. Many of the studies comparing the imaging techniques have included fewer than 50 patients and are thus unlikely to have adequate statistical power.

Technologies are constantly changing, with new techniques and equipment being introduced. By the time satisfactory numbers of patients have been recruited into prospective studies, techniques have often been superseded by newer, but unevaluated, developments. Many of the newer technologies have been developed in the USA. More research is required into the effectiveness of the more established imaging methods, with adequate patient numbers on UK patients, bearing in mind the cost-effectiveness of using these methods in the UK.

The accuracy of clinical staging is a major concern,[98,205,227,247] although this is not always acknowledged in studies of the reliability of clinical and pathological staging. Although these staging modalities can allow for generalised estimations of progression, for example, the use of tumour differentiation, these estimations are not specific enough to make accurate predictions for individual patients.

Clinical staging of prostate cancer is hampered by the lack of information relating to the natural history of the disease. Until there is a greater understanding of natural history, it is likely that staging will remain a relatively inaccurate process. In particular, further information is required with regard to T1 and T2 tumours.[202]

In the future, it is likely that further definitions of the T categories will be necessary, probably brought about by improvements in imaging techniques, particularly MRI.[202] Current imaging techniques are unable to differentiate between T2 and T3 tumours with sufficient accuracy.[202]

Clinical understaging often becomes apparent when specimens are examined pathologically or histologically.[222] The percentage of patients pathologically upstaged increases with the clinical stage of the disease, with up to 60% of men with clinical stage B2 disease [T1] upstaged after surgery.[206]

Tumour grading suffers from subjectivity, potential sampling errors, and the lack of a uniformly-accepted grading system.[248] Although tumour grade, volume and ploidy each correlate with the probability of metastasis, the correlations do not provide a definitive prediction.[248]

Chapter 5

Treatment

Three major types of treatment are recognised for localised prostate cancer: radical prostatectomy, radiotherapy, and conservative management. Hormone therapies tend to be reserved for cases with advanced or metastasised disease. With improvements in techniques and increases in the numbers of patients diagnosed with localised prostate cancer, the rates of radical treatment have increased markedly recently. Such increases have occurred despite the lack of evidence from randomised controlled trials concerning the effectiveness and cost-effectiveness of any of the treatments.

The majority of studies that have been conducted have tended to be observational in design. Such studies are inevitably subject to a number of biases which mean that their results need to be interpreted with caution. In addition, comparisons between the treatments are hampered by a number of factors including patient selection (those undergoing surgery, for example, tend to be younger and have fewer co-morbidities than those receiving radiotherapy or conservative management). Surgical series tend to include more patients with clearly confined disease, whereas patients with more advanced disease are often included in studies of men undergoing radiotherapy or conservative treatment. Differences in outcome between the treatments may also be related to understaging. Radical prostatectomy permits surgical staging of cases, whereas other treatments rely on clinical staging which may be very inaccurate.

There is a clear lack of rigorous studies of outcome following treatment for localised prostate cancer. Randomised controlled trials, (incorporating clinical effectiveness, patient perceived outcome, and cost) are urgently required.

Radical prostatectomy

Radical prostatectomy is increasingly becoming a treatment option for younger men diagnosed with localised prostate cancer. Recent rapid increases in the use of the procedure have occurred without the benefit of good quality evidence. In particular, evidence from recent, methodologically-sound, randomised controlled trials is lacking. Observational studies suggest that radical prostatectomy may offer slightly higher rates of survival than radiotherapy or conservative management for truly localised disease, although these studies are subject to a number of biases. In addition, a number of significant treatment complications are reported with radical prostatectomy, sometimes by high proportions of patients, including blood loss, incontinence and impotence. Clinicians are convinced that improvements in surgical techniques now result in increasingly fewer complications but there is little evidence to support this. Randomised controlled trials investigating long-, medium- and short-term outcome, including the effects of such complications on patients' quality of life, are urgently required.

Introduction

The first radical prostatectomy for the treatment of prostate cancer was performed 90 years ago. The operation remained unpopular for several decades as the complications were perceived to be worse than the disease.[249] During the past 15 years the procedure has become safer and more widely performed for prostate cancer,[250] due to improvements in surgical techniques (such as nerve-sparing) resulting in reduced blood loss[251] and fewer post-operative complications.[252]

Previously, radical prostatectomy was performed by a transperineal approach[253] but, in recent years, the retropubic or, less commonly, suprapubic approach has been favoured, usually preceded by pelvic lymph node dissection performed through a single incision. A perineal approach requires a separate incision for pelvic lymph node dissection but this approach has been revived with the use of laparoscopic lymphadenectomy, and the questioning of the need to carry out lymphadenectomy on **all** patients diagnosed with early confined prostate cancer.

As with other treatments, there is a lack of up-to-date, long-term[254] good quality evidence concerning the effectiveness of radical prostatectomy. Two RCTs have been published, but they relate to treatment in the 1980s and suffer from a number of methodological flaws (see below). The remaining evidence comes from a number of retrospective studies (see below). Three RCTs are currently underway, but all are experiencing problems with recruitment of patients.

The crucial issue with radical prostatectomy is whether or not early intervention in men with localised tumours reduces mortality from prostate cancer. This apparently simple issue conceals a plethora of confounding factors. As indicated in Chapter 2, the natural history of prostate cancer is uncertain, making it difficult to attribute survival directly to intervention without a large study comprising patients randomised to radical prostatectomy or conservative management.

In addition, problems with the accuracy of staging mean that some men considered to have clinically localised disease are found to have local progression when they undergo radical prostatectomy.

Other factors that need to be taken into account in any consideration of the effectiveness of radical prostatectomy are the morbidity and effects on quality of life caused by the operation itself. Radical prostatectomy is a major surgical procedure, and carries with it the risk of death and a number of serious complications, including incontinence and impotence. The effects on quality of life are largely unknown and this represents a significantly under-researched area.

Treatment rates

It is interesting to note that the number of radical prostatectomies performed has increased rapidly in the late 1980s and into the 1990s, in spite of the lack of evidence proving its effectiveness.

In the USA, for example, the age-adjusted proportion of men who received radical prostatectomy increased in all regions between 1984 and 1991 – from 11% to 32.2%, with the proportion receiving radiation treatment rising only a little, from 27% to 29.7%.[53] The absolute numbers treated also increased dramatically from 640 radical prostatectomies to 4806 by 1991. Radical prostatectomy progressively increased to, and then surpassed, radiotherapy in the management of local/regional prostate cancer. Also from the USA comes evidence suggesting substantial geographical variations in radical prostatectomy.[53] A population-based cohort study in Wisconsin, USA, for example, showed that the annual number of radical prostatectomies rose by 226% (from 283 to 922 operations) between 1989 and 1991.[255] In the combined areas sampled, the age-adjusted rate of radical prostatectomy grew from 25.1 per 100,000 in 1983 to 98.4 in 1989.[41]

Techniques of radical prostatectomy

There is considerable debate concerning the optimum method of carrying out a radical prostatectomy. Evidence in the published literature is somewhat scarce.

Nerve sparing

The aim of the nerve-sparing radical prostatectomy technique, introduced by Walsh in 1983, is to spare one or both of the neurovascular bundles that carry the nerves required to preserve potency. Men undergoing nerve-sparing, retropubic prostatectomy have a greater chance of erectile return post-operatively, particularly those under the age of 60 years.[256]

Nerve-sparing has been reported to result in a reduced blood loss and improved continence rates compared to the standard retropubic approach,[254] but critics of the nerve-sparing technique suggest that preservation of potency may compromise control of the tumour,[257] particularly in stage T2 disease.[257,258] Preservation of one neurovascular bundle may be performed on the non-palpable side in patients with T2 disease. However, 89% of patients with unilateral palpable tumours, in T2 disease, have been reported to have pathologically bilateral cancer; in a small series of patients who had three positive biopsies on only one side of the prostate, 85% were found to have tumour in the contralateral side.[258] Thus, with the possibility of positive margins, there is a risk in preservation of the contralateral neurovascular bundle in T2 disease, when relying only on clinical factors.

There are little long-term data available on outcome following use of the nerve-sparing technique.

Retropubic versus perineal approach

There is a lack of agreement between studies assessing the appropriateness of the two major approaches – retropubic and perineal.

Two retrospective studies have directly compared the safety, efficacy and morbidity following radical retropubic and the earlier technique of perineal prostatectomy, in 71[259] and 173[260] men. A significantly greater number of blood transfusions and a longer operative time in the retropubic group were reported in both studies. There were conflicting results in the number of days spent in hospital, with Frazier and colleagues reporting the retropubic approach resulting in a shorter hospital stay and Haab and colleagues the reverse. At 3 months after surgery, there was a greater reported level of impotence and incontinence among the perineal group. By 6 months there was no difference in continence rates between the two groups.[259]

Pelvic lymph node dissection

In the majority of cases radical prostatectomy is preceded by pelvic lymphadenectomy to assess the degree of local extension of the disease. It is claimed that cure is unlikely to be achieved in patients with lymph node involvement. In patients with clinically localised disease, reports of lymph node involvement range from 7.4% to 11%.[242,257,261] Walsh and colleagues[257] reported that every patient in their series with positive pelvic lymph nodes at prostatectomy had an abnormal PSA test within 10 years.

The perineal approach fell out of favour due to the need for a second incision for pelvic lymph node dissection.[262,263] Now, laparoscopic lymph node dissection combined with radical perineal prostatectomy is an established approach. Two retrospective studies have reported outcome results on this procedure but the small number of patients in each (37[264] and 31[262]) make comparisons of outcome and complication rates unreliable. A further study compared retropubic or perineal surgery in conjunction with laparoscopic pelvic lymph node dissection or standard open lymphadenectomy.[263] An evaluation was made of 76 patients with localised disease. Patients undergoing the laparoscopic lymphadenectomy with perineal prostatectomy experienced significantly less bleeding, fewer blood transfusions and a shorter hospital stay than the alternative approaches, and a significantly shorter operation time than the retropubic approach ($p < 0.001$). There were no significant differences in post-operative analgesic requirements, urinary continence or potency between the three approaches.

New approaches

In the USA, the effects of placing radioactive seed implants into the patient at the time of radical prostatectomy have been assessed in men with clinically localised prostate cancer.[265] Cancer-specific survival free of disease at 5 years was 100% for clinical stage A2 [T2, T3], 91% for B1 [T2a, T2b] and 75% for B2 [T2c] cancers. Ten-year survival figures were 100%, 82% and 68%, respectively.[265] Prospective studies on larger numbers of patients need to be conducted to establish the effectiveness of combining these two forms of therapy, both of which carry the potential for serious complications.

The effectiveness of radical prostatectomy

As indicated above, there have been only two published RCTs assessing survival following radical prostatectomy. Both of these trials suffer from a number of methodological flaws which are considered in some detail below (pp.39–40) and which preclude any firm conclusions based on their results. The remaining evidence comes from retrospective studies.

Randomised controlled trials

An RCT of radical prostatectomy or radiotherapy in men with T1/T2 prostate cancer was conducted in the early 1980s. The number of patients recruited was small (97), randomisation was unequal (58% assigned to radiation, 42% to surgery) and an intention to treat analysis was not conducted.[266] During the follow-up period, 10% of the surgically-treated men and 30% of the radiation-treated men were reported to have disease recurrence (the exact period of follow-up was unclear). Thus, the conclusion was drawn that radical surgery led to a better outcome. There were, however, a number of methodological flaws in this study. The impact of treatment was assessed with the first evidence of treatment failure as the endpoint; thus, long-term outcome was not evaluated. The trial was conducted prior to the introduction of PSA testing and, as DRE was not used to assess for treatment failure, patients with local recurrence may have been missed.[266]

Madsen and colleagues[267,268] report the 15-year follow-up of the well-known American Veterans Administration Co-operative Urological Research Group (VACURG)[269] prospective randomised study of radical prostatectomy with placebo against placebo alone. In this study, 142 patients with stages T1 and T2 previously-untreated prostate cancer were enrolled. Patients were randomly assigned to either radical prostatectomy followed by daily oral placebo, or daily oral placebo with no operation. Of the randomised patients, 27% were excluded either due to refusal of treatment, mis-staging or other protocol violations. The principal endpoints measured were time-to-progression and survival from all causes of death. Progression of disease was defined as occurring at the time of first metastases, at the first rise of prostatic acid phosphatase (PAP) to 2.0 KAU or death due to prostate cancer.

After a median of 7 years follow up, 14% of patients showed evidence of disease progression, seven patients in the prostatectomy group (six with metastases) and nine patients in the placebo group (three with metastases). Survival curves for all causes of death suggested that survival for patients with pre-operative palpable tumours was better in the prostatectomy group. However, specific figures were not reported.[270] At 15-year follow-up, neither stage nor treatment was found to be predictive of outcome but no data were reported.[268]

The results of this study should be interpreted with caution as there were serious flaws in the methodology. The number of patients included in the trial was small and the numbers randomised to each arm were unequal which prevented the detection of small to moderate differences between the groups. The study did not have sufficient statistical power to detect differences in cancer-specific survival between the groups. Of the patients initially randomised, [54] had clinical stage T1 disease. It is not clear what proportion had stage T1a disease, which would have been much less likely to progress with or without surgical intervention. The trial was conducted prior to the introduction of PSA testing and, as DRE was not conducted to assess for disease progression, a number of patients with localised recurrence may have been missed. There was an imbalance in the age distribution between the two treatment groups, with more elderly patients in the placebo group. The drop-out rate was high, and intention-to-treat analysis was not performed.

Two further RCTs are currently underway.

One is the Department of Veterans Affairs and the National Cancer Institute Cancer Therapy Evaluation Program co-operative study No. 407: Prostate cancer Intervention Versus Observation Trial (PIVOT).[271] This aims to determine whether early intervention with radical prostatectomy reduces all cause and prostate cancer-specific morbidity and mortality compared with expectant management. Recruitment began in 1994 with the aim of recruiting 2000 participants, and includes men of 75 years or younger with clinically localised (T1/T2, NX, M0) prostate cancer. Those with high surgical risk or a life expectancy of less than 10 years are excluded. The purpose of the study is to determine which of the two strategies is superior for managing clinically-localised prostate cancer.[272] Men are randomised to receive either radical prostatectomy with intervention for disease persistence or recurrence; or expectant management with palliative therapy reserved for symptomatic or metastatic disease progression. Patients will be followed up for between 12 and 15 years. The study is experiencing recruitment difficulties, however, because review of patients under expectant management is not allowed until the PSA level reaches 100 – a level which is unacceptable to many clinicians.

In the UK, an RCT funded by the MRC of total prostatectomy, radiotherapy and conservative management (PRO6) is currently underway for newly-diagnosed patients with T1 and T2 prostate cancer. Following diagnosis, patients are randomised into one of the three groups. To allow for an element of clinician and patient preference, randomisation occurs between two of the three arms, determined by each patients' circumstances. This may result in an element of selection bias. The aim is to recruit 1800 patients within a 3-year period and to monitor them until death. The study is experiencing severe recruitment problems, in particular because it is reliant upon an unpredictable supply of incidentally-diagnosed patients, and also because of clinician and patient reluctance to randomise between the defined groups.

Other studies

A structured literature review of treatment for localised prostate cancer was carried out of papers published between 1966 and 1991.[273] Out of 1600 English language articles, 144 were systematically assessed and reviewed. The authors concluded that radical prostatectomy was associated with fewer complications, but were unable to determine the effectiveness of the procedure because of serious flaws in the studies, particularly in the accuracy of follow-up and lack of stratification of patients by age and grade of malignancy.[273]

Several retrospective series of men undergoing radical prostatectomy have been published. A majority of these are American,[210,237,251,257,260,274–285] the rest being European[242,286–290] apart from one study from Israel.[253] The majority of these studies are based on a series of patients operated on within a single hospital, thus limiting their generalisability. There are also a range of methodological differences between the studies which impact upon the results, including different patient selection criteria (inclusion or exclusion of patients with tumour extension),[253,291] operative techniques, post-operative assessments, length of follow-up and methods of data analysis. Imbalances in patient selection are particularly common, including different substages, gradings of initial PSA, nodal status, and age.[292] It is possible, therefore, to make only loose comparisons between studies.

Survival and progression

Studies vary considerably in their presentation of survival and progression data. Several studies have used actuarial analyses (Kaplan-Meier survival curves) to predict the likelihood of disease progression following surgery.[210,251,257,261,280,293] However, the type of survival figures presented vary between studies, including overall survival, cause-specific survival (survival without death from prostate cancer), progression-free survival, metastases-free survival and survival free of local recurrence. These differences make direct comparisons between studies difficult. Local recurrence is also variably defined, with some studies relying on DRE and others on PSA rates.

Tables 13 and *14* summarise the various methods of presenting survival analyses. These suggest that cause-specific survival is between 86% and 91% at 10 years following radical prostatectomy in men with clinically localised disease. Freedom from clinical evidence of disease at 10 years ranges from 57% to 83%. Variation in these figures is most probably due to the different ratios of men with capsular penetration included in these studies (see *Table 15*). Few studies present sub-group analysis by stage. However, when the population is subdivided according to initial local extent of the disease, survival between the groups differs significantly ($p = 0.03$).[278]

Tumour stage has been shown, in some studies, to be related to the risk of progression following surgery. In a retrospective analysis of 186 patients undergoing radical prostatectomy in the USA, only one (3%) of the patients with stage A [T1] tumours had died of prostate cancer at 10 years, whereas of those with stage B [T2] tumours, 19% have died of prostate cancer and 49% are alive and apparently

TABLE 13 *Actuarial survival analysis at 10 years after radical prostatectomy for clinically-localised disease*

Study	Country	No of patients	Clinical stage/ grade/size of tumour	10-year survival (%)			
				Cause specific*	Metastases free	Clinical disease free	PSA disease free
Stein[278]	USA	230		91 (± 4.7)		72	
Zincke[251]	USA	3170	T1–T2c	90 (± 1.0)	82 (± 1.2)	83 (± 1.2)	
Fowler[359]	USA	138	A2–B	86	85	57	34
Walsh[257]	USA	955		83		70	
Norberg[261]	USA	19 19 12 24 12 15	Gleason 2–5 Gleason 6 Gleason < 7 < 2 cc 2–4 cc > 4 cc	90 84 44 92 47 73			
Morton[293]**	USA	586		97	93		90
Ohori[280]	USA	500		73 76 (5 years)			

* *Survival without death from prostate cancer*
** *5-year survival analysis*

TABLE 14 *Disease progression after radical prostatectomy in patients with clinically localised disease*

Study	Country	No of patients	Mean follow-up period (years)	Disease progression (%)	Died of prostate cancer (%)	Died of other causes (%)
Frohmuller[289]	Germany	100	15	32		
Mor[253]	Israel	100	1.5	6	0	0
Epstein[360]	Israel	507	4	23.8		
Stein[278]	USA	230	3	13	1.7	5.2
Zincke[251]	USA	3170	5		5	8.8
Fowler[359]	USA	138	5	28.9	6.5	13.7
Trepasso[281]	USA	601	3	12.4	1.9	2.9
Smith[237]	USA	186	10 years	13	22	18

TABLE 15 Degree of tumour extension at radical prostatectomy

Study	No of patients	Country	% organ-confined	% capsular penetration	% seminal vesicle involvement	Pre-operative clinical stage
Fromuller[289]	100	Germany	68	23		
Frohmuller[290]	115	Germany	81	—— 19 ——		Unspecified
Hautmann[287]	418	Germany	41.5	—— 58.5 ——		T1–T3
Pedersen[242]	182	Sweden	35	40	16	T1–T3
Stein[278]	230	USA	50	36	14	A1–B2
Ohori[280]	500	USA	45	47	17	T1–T3
Zincke[251]	3170	USA	47	—— 42 ——		T1–T2c
Walsh[257]	955	USA	37	48	7	T1–T2
Trepasso[281]	601	USA	49	36	15	T1–T2
Smith[237]	186	USA	58	30	12	A–B
Zincke[210]	148	USA	74	—— 26 ——		A
Frazier[282]	226	USA	45		25.6	T1–T2
Epstein[283]	157	USA	51		6	T1c

tumour free.[237] The relationship between stage and progression has been confirmed in other studies[210,261,293,294] but found not to be a significant predictor of progression in others.[251]

Tumour differentiation has been reported to be a much more accurate predictor of progression than stage. A Gleason sum score greater than 7 places the patient at greater risk of progression ($p = 0.83$).[237,261,278,285,294] In one retrospective series, only 23% of the patients whose Gleason score was 7 or less had evidence of disease progression at 10 years, whereas 80% of those with a Gleason score of 7 or more had progressed.[294] In another, men with poorly differentiated tumours (Gleason score of 8 or more) experienced the most significant excess mortality compared with a cohort of men without prostate cancer, while men with well-differentiated tumours did not have excess mortality.[285]

Further studies have confirmed the association between less well-differentiated tumours and more rapid tumour progression.[242,251,280] The reason for this is most likely to be that poorly differentiated cancers usually extend outside the prostate by the time they are detected, and progress rapidly.[280]

The probability of non-progression remains relatively constant for patients with impalpable cancer, but decreases consistently over time for patients with palpable disease.[254,295] Survival rates were higher for those with smaller tumours.[261] Age does not appear to be related to time to disease progression.[278]

When PSA level is used as a measure of progression, fewer men appear to have disease-free survival. Zincke reported 10 and 15 year figures for survival free of local and metastatic recurrence of 72% (± 1.4) and 61% (± 2.1) respectively. When a PSA level greater than 0.2 ng/ml was added, corresponding figures fell to 52% (± 1.4) and 40% (± 1.9), respectively.[251]

PSA level is often raised prior to clinical detection of disease progression in men having undergone radical prostatectomy. In Walsh's study, 70% were found to have an undetectable PSA after 10 years, with 23% having an elevated level of PSA.[257] When disease was organ-confined, this figure rose to 85%, but with evidence of seminal vesicle involvement it reduced to 43%.[257] Some 7% of the patients progressed to metastases, with 4% having local recurrence.[257]

Some men will go on to develop clinical progression and others will not.[278] For example, in one study, 36% of the radical prostatectomy patients who had pre-operative PSA levels measured had a raised PSA (> 4.0 ng/ml) post-operatively. Clinical progression had occurred in only 22% of these men at the time of the last follow-up.[281] However, it is impossible to determine whether some of these men will remain clinically progression-free with a raised PSA, or whether a raised PSA is a clear determinant of later clinical progression. This could only be determined by following all patients until death.

There is some evidence to suggest that there has been an improvement in average clinical outcomes in more recent years. A long-term follow-up study by Trepasso and colleagues divided patients treated with radical prostatectomy into two groups, those treated between 1972 and 1986, and those treated between 1987 and 1992. Analysis comparing the outcome between the two groups showed that there was a significantly lower rate of clinical failure in the latter group of patients at 5 and 6 years after prostatectomy.[284] There may be several explanations. First, with the advances in screening and diagnostic techniques, patients are being operated on earlier in the disease process. Second, there have been overall improvements in surgical techniques in recent years. Third, there is likely to be improvement in an individual surgeon's technique over time.

Extra-capsular extension. Local recurrence after radical prostatectomy reflects incomplete removal of benign or neoplastic cells.[296] The presence of positive surgical margins in the prostatectomy specimen is indicative of capsular penetration, signifying a tumour that has not been totally eradicated. Patients with seminal vesicle invasion, positive surgical margins, poorly differentiated tumours or capsular penetration are at increased risk for local recurrence (see *Table 15*).

Pathological stage is associated with rate of progression following radical prostatectomy. Stein and colleagues showed a significant association between degree of local tumour extension and time to disease progression ($p = 0.01$).[278] Men with confined disease have a survival rate superior to that of a male age-matched control population. This may be explained because men undergoing radical surgery are likely to be reasonably fit and without severe heart disease. They are thus likely to have a greater than average life expectancy. In addition, men with malignant conditions are usually followed-up more thoroughly than men in the general population.[290]

Poorly differentiated tumours (i.e. those with a Gleason score of 7 or greater) are rarely confined to the prostate and tend to progress faster than well differentiated tumours. A study by Ohori and colleagues on 500 men undergoing radical prostatectomy with clinically localised prostate cancer, identified those with poorly differentiated tumours.[280] Only 28% of these were subsequently found to be confined to the prostate. However, at follow-up, progression rate was strongly influenced by grade when the tumour extended outside the prostate ($p < 0.00005$). This suggests that poorly differentiated tumours can be controlled if they are identified while still confined to the prostate. The difficulty comes in identifying, from clinical factors, which patients have confined disease. The authors went on to analyse clinical factors in a subset of 427 men in their series. They reported that non-palpable cancer detected by an elevated PSA level was more likely to be poorly differentiated but confined to the prostate than palpable tumours ($p < 0.01$), particularly when the PSA level was less than 20. Confined tumours were not found when the Gleason score was 8 or higher.[280]

The risk of positive margins increase with tumour stage.[234] The proportion of men with capsular penetration (23–58%) and seminal vesicle involvement (7–25%) varies widely between studies.[237,257,278,280–283,287,289] There does not appear to be a clear reason for this. Radical excision in men with capsular penetration often means that the tumour will be completely removed. Disease progression rates are much higher in men with disease extension outside the prostate gland.[265,278,280,290]

Clinical stage A [T1] tumours and progression. The appropriate treatment of stage A [T1] disease is controversial. The decision whether to treat aggressively depends, for many clinicians, on the determination of the local extent or differentiation of the tumour.[210]

One study has examined pathological stage and outcome in patients with stage A [T1] tumours.[210] A US series of 148 men with stage A [T1] tumours underwent radical prostatectomy. Of the 32 men with clinical stage A1 [T1, T2] tumours, 63% had pathological stage A1 or A2 [T1, T2, T3] disease and 12% had extracapsular disease. Of the 116 men with clinical stage A2 [T2, T3] disease, 62% had pathologically confined disease and 29% had pathological stage C [T3] disease or higher. Of the men with extracapsular extension, 60% had Gleason grade 3 disease, none had grade 1. Progression occurred in few patients (one with clinical stage A1 [T1, T2], and eight with stage A2 [T2, T3]). Thus, locally advanced disease may be found in men with incidentally detected prostate cancer. Results from this preliminary study suggest a low progression rate following early treatment with radical prostatectomy. Further studies are required in this patient population to determine treatment effectiveness for stage A [T1] tumours.

Treatment complications

Complication rates have been reported to have reduced in recent years, although there is no clear evidence for this. Many clinicians believe, however, that improvements in surgical techniques have led to lower complication rates than are reported in the literature. For example, the incidence of deep venous thrombosis is declining and this has been attributed to preoperative prophylaxis and shorter operative times in recent years.[181]

Many papers have reported post-operative complication rates but there are differences in what is actually recorded and reported as a complication. Some reports distinguish between early and late complications while others distinguish between major and minor complications.[277] Typically, what is included within these definitions varies.

Early complication rates (up to 30 days following surgery) range from 7% to 16%[242,253,284,286] and late complication rates (30 days or more following surgery) from 1% to 14% (excluding loss of potency), the majority of which relate to continence.[242] Early and late complication rates are presented in *Tables 16* to *19*. There does not appear to be a significant association between the rate of early complications and age,[284] probably due to the highly selected population of men undergoing this procedure (i.e. fit and usually under age 75), or mode of diagnosis or pathological stage.[284]

Licht and colleagues examined rates of post-operative complications between early discharge after radical retropubic prostatectomy with standard discharge.[297] They reported no difference in complication rates between the two groups. This study should be interpreted with caution as the early discharge cases were all performed after the standard discharge cases, so improvement in operative technique could have accounted for the lack of difference in complication rates. Prior prostatic surgery, such as TURP, has been reported to increase the technical difficulty of performing radical prostatectomy; however, this has not been upheld in the recent literature.[258]

One study in the USA reported on interviews with a sample of men in the Medicare programme who had undergone radical prostatectomy between 1988 and 1990 to determine levels of incontinence and impotence.[298] This study is important because it examines outcome from the patient's perspective.

Treatment complications more commonly reported include operative and post-operative mortality, blood loss, deterioration in sexual function and incontinence.

Mortality. Deaths have been reported during the post-operative period at the rate of 0.2–1.2%.[210,242,260,276,277,284,286,287] In all cases the cause of death was cardio-pulmonary.

TABLE 16 *Early complications following retropubic prostatectomy (excluding impotence and incontinence)*

Study	Country	No of patients	Complications (%)					
			Cardiovascular/ thrombo-embolic	Wound	Rectal injury	Lymphocele	Other	Death
Rossignol[286]	France	429	3.3			3	1.8	0.2
Hautmann[287]	Germany	418	3.8	4.3	2.9	6.6	4.4	1.2
Pedersen[242]	Sweden	182	7.1	6	1	1	0	0.6
Mor[253]	Israel	100	2	1	1	1	3	0
Andriole[284]	US	1324	4	1.3			2.1	0.2
Stein[278]	US	230	3.9	0.9	0	1.3	1.3	0
Ritchie[277]	US	100	2	2	0	3	2	1
Igel[276]	US	692	4.7	1.7	1.3	0.9	20.5	0.6
Frazier[260]	US	173	1.2	1.2	0	0	1.7	0.6
Zincke[210]	US	148						0.6

TABLE 17 *Post-operative potency following radical prostatectomy*

Study	**Country**	**Surgical technique**	**No of patients**	**Potency, 6 months post-operative**				**Potency, 18 months post-operative**			
				(a)	**(b)**	**(c)**	**(d)**	**(a)**	**(b)**	**(c)**	**(d)**
Rossignol[286]	France	Retropubic, 100% nerve sparing	85	73%			100%	85%			64%
Pedersen[242]	Sweden	Retropubic, nerve sparing	182, 126 (potent pre-op)					19% of 126			
Mor[253]	Israel	Retropubic	100	20%		80%	60%				
Jonler[279]	USA	Retropubic	86 (84%) (potent pre-op)					9%	38%	51%	
Leandri[361]		Retropubic	620	30%	38%	32%	63%	56%	16%	28%	63%
Catalona[274]	USA	Retropubic, nerve sparing	295					59%			100%

(a) Full potency, (b) Partial potency, (c) Total impotence, (d) Percentage of patients assessed.

TABLE 18 *Post-operative continence rates following radical prostatectomy*

Study	**Country**	**Surgical technique**	**% nerve sparing**	**No of patients**	**Continence within 6 months post-operative**				**Continence within 18 months post-operative**			
					(a)	**(b)**	**(c)**	**(d)**	**(a)**	**(b)**	**(c)**	**(d)**
Rossignol[286]	France	Retropubic	27	429	86%	13.8%	0	89%	93%	6.2%	0	60%
Hautmann[287]	Germany	Retropubic		418					81%		0.9%	84%
Huland[288]	Germany	Unspecified		214	85%		15%	77%	93%		7%	63%
Pedersen[242]	Sweden	Retropubic	Yes	182					79%	19%	1%	93%
Ramon[258]		Retropubic	21	484	90%	10%	0	100%	95%	5%	0	82%
Mor[253]	Israel	Retropubic		100	87%	8%	1%	96%				
Catalona[295]	USA	Retropubic		435					94%		6%	100%
Myers[275]	USA	Retropubic	65	172	87%			99%	94%			99%
Zincke[210]	USA	Retropubic		148							9%	100%
Igel[276]	USA	Retropubic	667						75%	21%	2%	99%
Ritchie[277]	USA	Retropubic	38	100					27%	72%	0	99%
Leandri[361]		Retropubic		620	70%	8%	0	78%	60%	4%	0	64%
Stein[278]	USA	Retropubic	61	230						10%	2%	unspec.

(a) Continence, (b) Mild incontinence, (c) Total incontinence, (d) Percentage of patients assessed.

Blood loss. It is suggested that there has been a reduction in average blood loss during retropubic prostatectomy in recent years,[251] but there is wide variation in the literature in the reported average rates of blood loss, varying between 100 and 2000 ml.[260,276,286,287,291]

Sexual function. There are several factors which have been shown to affect post-operative sexual function, including age, pre-operative potency, clinical and pathological stage and surgical technique (i.e. preservation or excision of the neurovascular bundle).[274,286,299] (See *Table 17*). Fewer men

***TABLE 19** Late complications (those occurring 30 days or more after surgery) following radical prostatectomy, excluding incontinence and impotence*

Study	Country	Surgical approach	No of patients	Complications	%
Leandri[361]		Retropubic	620	Bladder neck contracture Post-operative scar hernia, repaired surgically Hydrocele, repaired surgically	0.48 0.32 0.48
Stein[278]	USA	Retropubic	230	Urethral stricture	6.5
Frazier[260]	USA	Retropubic and perineal	173	Anastomotic stricture Bladder stones Urethrorectal fistula	6.9 0.6 0.6
Mor[253]	Israel	Retropubic	100	Vesicourethral stenosis	2
Hautmann[287]	Germany	Retropubic	418	Anastomotic stricture Urethral stricture	8.6 4.1
Pedersen[242]	Sweden	Retropubic	182	Bladder neck stenosis	13

had return of erection after unilateral nerve sparing prostatectomy compared with those undergoing the bilateral technique.[274] However, more advanced disease in the former group may explain this difference.

Several studies have examined the rates of impotence following radical prostatectomy (see *Table 17*). Most studies have not assessed pre-operative potency levels for comparison, and there are differences between the studies in their definitions of potency and impotence, as well as different methods of evaluation.

Interviews with Medicare men who had prostatectomy revealed that 61% of those who said they were sexually active before surgery could not have satisfactory erections after the operation, with only 11% reporting erections firm enough for intercourse.[298]

Age, clinical and pathological stage, and surgical technique correlated with return of sexual function.[299] In men less than 50 years old, potency was similar in patients who had both neurovascular bundles preserved (90%) and patients who had one neurovascular bundle widely excised (91%). In men over the age of 50 years, sexual function was better in patients in whom both neurovascular bundles were preserved than in those in whom one neurovascular bundle was excised ($p < 0.05$). When the relative risk of post-operative impotence was adjusted for age, the risk of impotence was five-fold greater if there was capsular penetration or seminal vesicle invasion, or if one neurovascular bundle was excised ($p < 0.05$). Subjective assessment of potency over 12 months since surgery in a survey study revealed that 51% of patients felt that their sexual function after surgery was a substantial problem.[279] However, age was not a significant factor in the ability to have erections after surgery in this study.

Post-operative potency has been shown to be related to pathological stage, with the proportion of men retaining full potency declining with increasing extent of the tumour.[277] This is most probably related to the fact that the sparing of the neurovascular bundles is less likely to be performed in men with higher stage tumours.

Incontinence. There are wide variations in the definitions and assessments of continence between studies (see *Table 18*). Stress incontinence was, for example, usually assessed, but ‘dribbling’, which may potentially be as embarrassing, was not always considered. Definitions of incontinence were extremely variable – in one study, the placement of an artificial sphincter and the use of more than two incontinence pads per day was considered to be indicative of stress incontinence,[300] whilst in another study, the use of one pad per day was reported as ‘incontinence’.[274] Other studies distinguish between ‘total’ and ‘partial’ incontinence.

A number of reasons for post-prostatectomy incontinence have been suggested, including sphincter damage, detrusor instability, urinary tract infection, anastomotic stricture, vesical neck contracture, retained sutures, neurological conditions and urinary retention with overflow.[301] The reported incidence of incontinence after radical prostatectomy varies widely, ranging from 4% to 21% for mild or stress incontinence, and from 0% to 7% for total incontinence by 18 months post-operatively (see *Table 18*). Post-operative incontinence is a distressing complication, often causing social and psychological problems to the patient, and is difficult to treat.[300] Advances in surgical techniques have clearly improved the post-operative continence rates. A comparison of continence rates between studies does not reveal a clear benefit from the performance of a nerve-sparing technique (see *Table 18*). No significant correlation has been shown between pathological stage or the performance of nerve sparing surgery and recovery of continence.[274]

Dribbling is a major problem for a high proportion of patients post-operatively (59%[279]). Whether and to what extent this may be caused by surgery or be a consequence of BPH is unknown. Age has been reported to be a significant predictor of continence, with post operative continence being achieved less often as age increased.[274,286,288,302] Pre-operative urodynamic assessments indicated that men at increased risk of post-operative incontinence were more than 70 years old, with a low maximal urethral closure pressure with and without voluntary contraction.[288] The numbers in this study were, however, small and further data are required for convincing evidence.

Interviews with Medicare men 2–4 years after their radical prostatectomies showed that, for many men, incontinence can be a persistent problem. Some 19% reported that they had originally had problems with dripping of urine but that these had later resolved;[298] 34% reported that they still had problems with dripping, and a further 32% indicated that the problems were so severe that they had to use pads or clamps.[298]

One clinical method of improving post-operative incontinence has been reported, the injection of polytetrafluoroethylene paste, but it has poor results.[303]

Despite reported improvements in surgical technique, incontinence remains a significant long-term problem for many patients after radical prostatectomy. Standardised methods of evaluation are urgently required.

Quality of life

Evidence on quality of life following radical prostatectomy is extremely scarce. Only two studies have been conducted specifically aiming to assess quality of life in this group of patients. Herr and colleagues[304] reported on a series of 50 patients who were assessed, by self-administered questionnaire, on the impact of urinary incontinence on their quality of life post-operatively. Level of continence varied between patients, but all patients wore pads (an average of three per day). A quarter of the patients reported being extremely upset about their level of incontinence, reporting limitations in daily exercise and long-distance travel. More than three-quarters of the patients evaluated less than 5 years post-operatively reported that they would choose surgery again, despite the incontinence, but only half of those evaluated after 5 years would do so again. For those who were incontinent for 5 or more years following surgery, satisfaction with outcome tended to diminish.[304]

In contrast, Pederson and colleagues conducted a prospective study, assessing patients' quality of life prior to and up to 18 months after surgery. In their study, level of continence did not cause an increase in distress to patients 3 months post-surgery.[305] The lack of detailed data concerning patients' continence status renders this study difficult to compare with the study by Herr.

Research into quality of life following clinical interventions such as radical prostatectomy will aid the clinician in helping patients to make informed decisions about their treatment. Quality of life in relation to sexual function following prostatectomy for prostate cancer has not been investigated. There has been little research into this area and, as yet, few conclusions can be drawn.

Conclusion

There is a lack of good quality data from RCTs on survival following radical prostatectomy. Evidence concerning radical prostatectomy is based largely upon retrospective observational series of men followed-up for varying periods, none of which have been performed in the UK. Conclusions from these, predominantly American, studies can only be tentative due to the differences in recruitment populations, staging, extracapsular disease, methods of assessment and types of data analysis.

Overall, the 10-year survival of men with confined disease is equivalent to, or in some cases better than, that of age-matched men in the population. For men with extracapsular disease, survival is lower, and depends on the degree of extracapsular extension. Tumour differentiation would appear to be a good predictor of disease progression following prostatectomy, with poorly differentiated tumours faring considerably worse than well or moderately differentiated tumours.

The overall survival figures are better for men treated with radical prostatectomy than for men managed conservatively. However, only loose comparisons can be made between these series of men, due to the differences in the ages and fitness of the men entered into these studies. Men undergoing radical prostatectomy for localised prostate cancer tend to be younger and fitter than men managed conservatively.

It has also been found that there is an increased risk of complications with age, particularly for men over the age of 75 years.[285] Modelling the effectiveness of treatment following a structured literature review indicated that the expected benefits of surgery decreased rapidly with increasing age, with only men aged 60–65 years likely to achieve benefit, even taking the most optimistic view of outcome.[306] If quality of life is taken into account, then quality-adjusted life expectancy is decreased for men aged 70 years and over.[306] This study also indicated that men with well-differentiated tumours were likely to suffer net harm from radical treatment, as were most sexually active men with moderately differentiated cancer.[285,306]

Approximately, 30% of patients undergoing radical surgery will experience a raised post-operative PSA level (> 4.0 ng/ml), but not all cases will result in clinical disease recurrence. For these men, it will not be clear whether they are free of the disease or whether a raised PSA level indicates the early stages of disease recurrence. Thus, the significance of PSA levels following surgery needs to be examined further, in order to reduce unnecessary patient anxiety.

Significant levels of post-operative complications have been reported in the literature, and these include long-term complications such as incontinence and impotence. With the introduction of PSA testing, men are being diagnosed and treated earlier in the disease course than previously. Thus there will be increasing numbers of younger men at risk from long-term complications from this procedure. There have been few studies examining the effects on quality of life of complications following surgery, and these are urgently required.

The number of radical prostatectomies being performed is clearly rising. It is, however, unclear whether variations in operative rates reflect differences in access to care or surgeon and patient preferences.[307] Without good trial evidence, the true benefit of radical surgery remains unclear in men with varying clinical and pathological stages of disease.

Radiotherapy

There has been a rapid rise in the use of radiotherapy for the radical treatment of localised prostate cancer during the 1980s and 1990s. The major technique used is external beam radiation, with radioactive seed implants and conformal radiotherapy currently under development, primarily in the USA. The majority of studies of outcome following radiotherapy are observational in design, making comparisons between studies difficult. Overall, it appears that survival and recurrence rates following radiotherapy are strongly related to grade and stage of disease. Patients with clearly organ-confined prostate cancer and well-differentiated tumours have significantly better outcome than those with higher stage and poorly differentiated disease. A number of acute and late complications arising from radiotherapy are also reported.

Introduction

Radium irradiation and X-rays were used as palliative treatments for the relief of pain in prostatic cancer from the 1930s onwards. In the 1960s, supervoltage radiotherapy was introduced using a high energy X-ray beam. More recently, there has been a dramatic increase in the use of radiotherapy across the USA and Europe. For example, at the Royal Marsden Hospital, Surrey, there was a 387% increase in the use of radical radiotherapy treatment in the period 1980–89 compared with the previous decade.[308]

Many prostate tumours are slow growing and maximal tumour responses with radiotherapy are achieved over a period, often 30–40 days.[308] It is necessary for the field set-up to be exactly reproducible, particularly the positioning of the patient, and this is typically achieved by using a body cradle cast. The rectal and vesicle mucosa, small bowel and femoral heads are the ‘organs at risk’ and are shielded. CT scans are used to define the treatment fields. The volume of the prostate and tumour are calculated and a planning target volume is calculated to guide the treatment. The radiation dose reported in US studies is usually between 60 and 70 Gy depending on the volume and stage of the tumour, and is slightly lower in the UK (50–60 Gy).[309,310]

There is also variation between the radiation fields treated. In several studies the pelvic lymph nodes have been included,[311] in others the seminal vesicles but not the lymph nodes are included[312,313] and, in many, only the prostate gland has been exposed to radiation treatment. The evidence concerning the therapeutic value of pelvic lymphadenectomy or external irradiation to the whole pelvis is still inconclusive.[314]

There is thus an urgent need to evaluate the available outcome data to determine the most effective and appropriate radiotherapy techniques, to define the optimal selection of patients for treatment, and to assess its use compared with other treatment modalities for men with prostate cancer. The major technique is external beam radiation, although there have been other developments, including radioactive seed implants and conformal radiotherapy.

External beam radiation

Randomised controlled trials

Only one RCT comparing radiotherapy with radical prostatectomy has been published.[266] Results from this trial suggested that radiotherapy was associated with a poorer outcome, but there were a number of methodological flaws in the study which limit its validity (for details, see above, pp.39–40).

No UK or European RCTs have been published in this area.

Observational studies

The majority of studies of outcome following radiotherapy are observational, and often retrospective in design. They are thus subject to a number of methodological weaknesses, including highly selected patient groups (such as those with metastases[315] undergoing endocrine therapy during or prior to radiation treatment,[315,316] and those undergoing TURP prior to therapy[315–317]), lack of specification of clinical stage, and variable definitions of outcome and follow up.

There is one study which provides observational data from an RCT. The US Radiotherapy Oncology Group trial (RTOG 77-06) recruited patients considered suitable for radical surgery for a trial comparing methods of determining nodal status.[318] These patients then went on to receive radiotherapy and, as there were no differences reported in outcome, the results of both arms were combined and presented.[318] At 5 years, 96% were free of isolated recurrence, with 87% in this position at 10 years, although the number followed for 10 years was small (n = 32).[318] Recurrence was associated with stage, with T2 patients experiencing a higher likelihood of local recurrence than T1.[318] Survival was reported to be higher than age-matched controls.[318] The authors selected patients who would be suitable for surgery, and so these results may be more comparable to radical prostatectomy studies than other radiotherapy series where patients tend to be older and less fit.

The majority of other radiotherapy outcome studies are also from the USA,[316–321] with a small number of studies from the UK[309,310] and Italy (*Table 20*).[315] Results show that patients with intracapsular disease or well-differentiated tumours have a significantly better survival than those with extracapsular disease and poorly differentiated tumours, and that disease progresses more rapidly in the latter group.[310,311,320] Patients with poorly differentiated tumours are significantly more likely to have a poorer survival than those with moderately

TABLE 20 *Outcome following external beam radiation in men with localised prostate cancer*

Study	Country	No of patients	Mean age	Clinical stage	Mean follow-up (months)	Disease free (%)	Local progression (%)	Distant metastases (%)	Died of prostate cancer (%)	Died of other causes (%)
Hanks[318]	USA	104	67 (50–81)	T1,T2	91.2 (12–133)	86	10	14	9	
Kuban[325]	USA	647	68 (46–86)	A2–C [T2,T3]	65 (3–180)	61	10	20		
Hanks[318]	USA	104	67	T1b–T2	7.6	85 (at 5 years) 67 (at 10 years)	93 (at 5 years) 87 (at 10 years)	10 (at 5 years) 21 (at 10 years)	8.6	not reported
El-Galley[309]	UK	191	68 (50–83)	T1–T4	40* (min of 12 months)		19	40		
Davies[310]	UK	105	68 (47–82)	T1–T4	168		4	36	30	19
Arcangeli[315]	Italy	199	69*	T1–T4 (43 pts T1–2)	60* (11–160)		23 (of T1–2)	28 (of T1–2)	28 (of T1–2)	12 (of T1–2)

* *Median value*

TABLE 21 Predicted survival for men treated with external beam radiation

Study	Country	No of patients	Clinical stage	Mean age	5-year overall survival		10-year overall survival	
Davies[310]	UK	105	T1–4	68	T2 (n = 47)	70%	T3 (n = 41)	51%
El-Galley[309]	UK	191	T1–4	68		63%*		35%*
Arcangeli[315]	Italy	199	T1–4	69	T1–2 (n = 43)	81%**	T1–2 (n = 43)	77%**
Hanks[318]	USA	104	T1b–T2	67		96%*		86%*
Lee[319]	USA	500	T1–4	70	T1 (n = 15)	85%		
					T2 (n = 17)	82%		
					T3 (n = 6)	66%		
					T4 (n = 0)	25%		
RTOG 77-06 (reported in [324])	USA	444	A2,B [T2]			85%		64%
Rosenzweig[322]		285	A2–C [T2,T3]		A2, B	63%**	A2, B	33%**
					C	40%	C	22%
Lai[317]	USA	191	B [T2]	68	66–85% (depending on therapy duration)		37–60% (depending on therapy duration)	
Hanks[318]	USA	104	T1,T2	67				86%
Duncan[316]	USA	411	T1 (n = 70)	65	T1	93%*	T1	79%*
			T2 (n = 341)		T2	92%*	T2	66%*
Perez[320]	USA	738	A–D1 [T1,T2,T3,M,N]		A2, B	76%**	A2, B	62%**
Ennis[321]	USA	289	A2–C [T2,T3]	69	A2–B	66%	A2–B	38%
					C	59%	C	21%

* *Cause specific survival*
** *Recurrence-free survival*

differentiated tumours ($p < 0.05$).[322,323] A UK study also supported this, with El-Galley and colleagues reporting Gleason grade and stage to be significantly associated with more rapid progression and development of distant metastases.[309]

A paper presenting long-term outcome data from the Patterns of Care Study and the Radiotherapy Oncology Group in the USA was published in 1994, with data on more than 3000 patients.[324] This analysis suggests cure of most patients with stage T1 cancer and approximately one-half of those with T2 disease.[324] Normal PSA levels were found in 88% after 10 years.[324]

Overall survival rates reported by these studies are difficult to compare because of the selection of patients and inclusion of patients with a range of grades and stages of prostate cancer. Five-year survival for patients with T1 or T2 disease averages around 70–80% (see *Table 21*). Survival rates for those with more extensive disease are much lower.

The likelihood of local and distant recurrence also increases with higher tumour stage and lower differentiation ($p < 0.01$).[325] In addition, the development of metastases is significantly greater for those with higher stage disease ($p < 0.001$).[325] Again, comparison between studies is difficult, but local progression for T1 or T2 disease appears to average around 10–20%, with the development of metastases higher, at between 20% and 40% (see *Table 20*).

The evaluation of recurrence has been confused by the inclusion of PSA levels in some studies but not others. In addition, there is debate concerning the levels of PSA, PSAD and PSA velocity which can be found following treatment, with several authors contending that PSA levels may be artificially raised during therapy, but are then likely to decline.[326–330] Poor outcome has been suggested in men with a PSA level greater than 4 ng/ml between 6 months and 5 years after radiotherapy.[330]

It has been claimed that outcome following radiotherapy is equal to that of radical prostatectomy at

10 years, although it is admitted that only an RCT will prove this.[324]

Radioactive seed implants and conformal radiotherapy

Radioactive seed implants, interstitial irradiation, or brachytherapy as it is sometimes termed, have been used in the treatment of prostate cancer since as early as 1910, and permanent gold-198 and iodine-125 implantation techniques have been used for localised disease over the last two decades. One advantage of this mode of therapy is the enhanced ability to distribute the radiation dose within the tissues of the prostate gland and adjacent soft tissues, while sparing surrounding radiosensitive normal organs such as the large bowel and bladder.[331]

Radioactive seeds are implanted in and around the prostate with a needle through a plastic template under direct vision on CT scan and palpation. Appropriate adjustments to the dosage are made by unloading the seeds (embedded in plastic ribbons) as required.[314]

Conformal radiotherapy involves the use of 3-D computer-assisted tomography to allow a more accurately directed beam configuration. This method has been piloted in the USA and is, as yet, unavailable in the UK. Results of preliminary studies show slightly improved morbidity in men with stage T1–T3 tumours compared with conventional radiotherapy.[332]

Outcome in localised disease

No RCTs have been conducted assessing the use of seed implants or conformal radiotherapy as a treatment, or in comparison with external beam radiation.

Some observational studies from the USA have attempted to evaluate seed implants, but these studies are difficult to compare as they are short term,[314] include unequal numbers of patients with localised and advanced disease,[333] or include patients with metastases.[314] In addition, many studies have used the seed implant technique in conjunction with external beam radiation, making assessment of independent outcome for this therapy difficult (see *Table 22*). The many studies including fewer than 50 patients have been excluded from this review as the sample sizes are too small to provide adequate results.

Similar survival rates have been reported as for external beam radiation above, with survival clearly related to grade and stage of disease[331] (see *Table 23*).

PSA levels have been reported to be reduced 3 months following therapy, and it has been suggested in one study that those with a PSA level of 0.5 ng/ml or lower had a significantly better

TABLE 22 *Predicted survival for men with combined radiotherapy*

Study	**No of patients**	**Country**	**Type of treatment**	**Mean age**	**Disease-free survival**		**Cancer-specific survival**	
					5 years (%)	**10 years (%)**	**5 years (%)**	**10 years (%)**
Khan[331]	321	USA	Seed implant + external beam	70	T1b 89.5 T2a 89.9 T2b 64.7 T3 44.8			
Holzman[336]	121	USA	Seed implant + external beam	63			83 ± 7	43 ± 14
Kwon[265]	80	USA	Seed implant + external beam	64	A2 [T2] 100 B1 [T2a,b] 91.1 B2 [T2c] 74.6	A2 100 B1 81.5 B2 67.8		

TABLE 23 *Outcome following seed implant and external beam therapy*

Study	**Country**	**No of patients**	**Mean age**	**Clinical stage**	**Mean follow-up (months)**	**Disease free (%)**	**Local progression (%)**	**Distant meta-stases (%)**	**Died of prostate cancer (%)**	**Died of other causes (%)**
Holzman[336]	USA	121	63	C [T3]	96	25	53	22	41	19
Kwon[265]	USA	80	64	A2–B2 [T2]	65		2.5	12.5	5	9

disease-free survival than those with higher PSA values ($p = 0.0001$).[334]

There have been no European studies assessing the effectiveness of radioactive seed implants. This treatment method is not popular in the UK following reports of high rates of post-treatment complications (see below). Early results showed poor outcome,[334] but the technique is gaining popularity in the USA.[335] Radioactive seed implants are currently available for only a small number of patients at a limited number of oncological centres in the UK.

Complications following radiotherapy

As with other modes of treatment there is considerable variation in the complications that are reported, with some studies reporting only severe complications[336] and other reporting all complications. Reported incidence of complications varies between 15% and 94%,[310,336,337] so only tentative comparisons can be made. The Radiotherapy Oncology Group and European Organisation for Research and Treatment of Cancer (EORTC) have developed a grading system for lower gastrointestinal and genitourinary acute sequelae,[338] but this does not appear to be widely used.

Acute complications from radiotherapy usually result from volume of tissue treated and relate to treatment technique. It is asserted that many acute complications can be expected to settle within 4–6 weeks of completing radiotherapy treatment.[308] Acute complications include rectal bleeding, cystitis, diarrhoea, proctitis, haematuria and skin reactions (see *Table 24*). It is clear, however, that many studies do not report acute complications.

Death as a direct result of treatment complications has occurred.[316] Urethral stricture has been suggested to occur slightly more often in patients with prostate cancer who have previously received TURP.[339] Impotence (variably defined) has been estimated to occur in 25–40% of treated patients, and usually develops during the 6 months after treatment.[308,314] One UK study reported higher levels of complications than other studies,[310] thought to be caused by the level of fractionation used. Late complications (occurring at least 3 months after treatment) may develop months or years after treatment, and include urethral and recto-anal stricture, rectal and bladder ulceration, chronic cystitis, urinary incontinence and impotence (see *Table 25*).

Long-term follow-up is required to assess the longer lasting complications associated with radiotherapy, which are usually the more severe complications. Earlier studies suggested that extending the radiation field to include the pelvic lymph nodes increases the morbidity without significantly increasing survival.[314]

Complication rates following combined seed implantation and external beam radiation have only been reported in the US literature (see *Table 26*).

TABLE 24 *Acute complications (within 3 months) following external beam radiation*

Study	No of patients	Country	Radiation dose (cGy)	Urinary frequency (%)	Diarrhoea (%)	Skin reactions (%)	Cystitis (%)	Proctitis (%)	Rectal bleeding (%)	Haematuria (%)	Other (%)
Davies[310]	105	UK	5100–6000	44	44	16	18				1
Greskovich[337]	289	USA	5858–6900		2		1	3	2	2	2

TABLE 25 *Late complication (after 3 months) following external beam radiation*

Study	No of patients	Country	Radiation dose (cGy)	Proctitis (%)	Urinary (%)	Impotence (%)	Urethral stricture (%)	Bowel complications (%)	Ano-rectal stricture (%)	Other (%)
Davies[310]	105	UK	5100–6000	29	10	4	2			1
El-Galley[309]	191	UK	5000–6000		36			36		
Arcangeli[315]	199	Italy	5000–7600	4.5	17.5		4	1.5	1	0
Greskovich[337]	289	USA	5858–6900	2	5		0.3	0.6	0.3	
Green[362]	321	USA	4500–6500			7				
Lai[317]	191	USA	6475–7420	4.7	7.3	14.6	5.2	2	0	4.7

TABLE 26 *Complication rates following combination therapy*

Study	No of patients	Country	Treatment	Rectal (%)	Urinary (%)	Urethral stricture (%)	Impotence (%)	Other (%)
Critz[334]	239	USA	Seed implant + external beam	23	13	1.2		0.4
Syed[314]	200	USA	Seed implant + external beam	8	2		25	0.5
Doornbos[340]	137	USA	Radical prostatectomy + seed implant	0.7	2			0.7
Khan[331]	321	USA	Seed implant + external beam	7	10	0.6		1.5
Priestly[335]	133	USA	Seed implant	0.7	0.7		< 10	
Holzman[336]	121	USA	Seed implant + external beam	4	25*	4		9

* *Including bladder outlet obstruction*

Some severe complications have been reported, including vesicorectal fistula and urethral stricture, as well as perineal pain and haemorragic cystitis.[340] Improvement in technique appears to play a part in reducing complication rates.[314]

Conclusion

As with radical prostatectomy, the probability of curative treatment following radiotherapy is highest for small-volume, relatively well-differentiated tumours. Survival rates following radiotherapy treatment are clearly related to grade and stage of disease. Overall, studies of radiotherapy have not been of the highest quality, with only one RCT. The majority of studies are observational, often retrospective, and with a number of variations and methodological flaws which make detailed comparisons difficult.

As with other treatment modalities, studies vary in the assessment of recurrence. More recent studies have included the use of PSA testing, which may have increased the number of patients found to have local recurrence compared with the palpable recurrence used in earlier studies.

Overall, evidence suggests that radical radiotherapy might be beneficial for patients aged 60–65 years, using the most optimistic view of outcome, but is likely to be harmful for older men.[306]

Conservative management

Conservative management has always been viewed as a treatment option for non-symptomatic patients with prostate cancer, particularly for older men. Increasingly, however, there are concerns about its suitability for men with localised disease, and its effectiveness compared with more radical treatments. Data primarily from observational studies suggest that conservative management may be most suitable for older men with low grade disease, who are most likely to die from causes other than prostate cancer. In younger men, and for those with higher grade disease, a relatively large proportion are likely to progress locally, with some developing metastases and dying of prostatic cancer. Informed patient choice between treatment options is probably the best current strategy. Randomised, controlled trials of conservative management compared with radical treatments are required for more definitive conclusions.

Introduction

Conservative management, also referred to as expectant management or 'watchful waiting' implies no active treatment until the patient experiences symptoms from outlet obstruction or metastatic disease. Patients undergoing conservative management are usually reviewed regularly to assess disease progression and discuss treatment options.[20]

Uncertainties about the natural history of prostate cancer, particularly the lack of knowledge concerning which tumours will progress, the general belief that many prostatic tumours do not progress[341], and the lack of data concerning the effectiveness of radical treatments (see above and below), suggest that conservative management should be considered to be a valuable management option.[342] Conservative management is used particularly for older men and those with more advanced disease. For men with localised disease, however, there is debate about who would benefit most from conservative management. It would clearly be the ideal treatment for those whose prostate cancer will not develop and who die from other causes. It is not yet possible, however, to predict whose tumours will progress. Those whose cancer progresses beyond the prostatic capsule during the period of conservative management will then be unable to have radical treatment.

The evaluation of the effectiveness of conservative management is also fraught with many difficulties. RCTs comparing conservative management with more active interventions for patients with localised prostate cancer have proved difficult to establish, primarily because of patient and clinician unwillingness to randomise such patients to no active treatment. The trials that have been established are described below.

A number of observational studies of conservative management patients have been undertaken (see below and *Tables 27* and *28*), although the majority suffer from the usual flaws of these studies: selection bias (often the oldest and sickest are offered conservative management), and variable methods of defining progression and follow-up.

The effectiveness of conservative management

Conservative management can be a treatment option for men with incidentally discovered

TABLE 27 *Outcome studies with patients undergoing conservative management for patients with localised disease*

Study (country)	Study design[†]	No of patients	Mean age at diagnosis	Length of follow-up (months)	Clinical stage	Disease progression (%)	Metastases (%)	Died of prostate cancer (%)	Died of other causes (%)
Whitmore[342] (USA)	R	75	B1 [T2a,b] 65 (54–77) B2 [T2c] 67 (59–82) B3 69 (63–81)	B1 133 (24–222) B2 130 (36–298) B3 108 (36–197)	B1 29 B2 37 B3[*] 9	B1 65.5 B2 78 B3 44	B1 6 B2 17 B3 2	B1 10 B2 43 B3 0	B1 13 B2 46 B3 33
Jones[350] (USA)	R	233	Unspecified	264	A1–B2 [T1–T2]	A1 0.4 A2 3	B1 1 B2 3	A1 6 A2 5	B1 2 B2 6
Johansson[343] (Sweden)	P	223		120	T0–2	34	12	8.5	47
Adolfsson[344] (Sweden)	P	122	Median 86 (38–89)	Median 91 (8–127)	T1–2	55	14	7	31
Waaler[345] (Norway)	R	94	73 (52–90)	108	T0–2	T0 focal 1 T0 diffuse 2 T1–2 7	T0 focal 0 T0 diffuse 7 T1–2 6	T0 focal 0 T0 diffuse 3 T1–2 6	33
George[19] (UK)	P	120	74 (62–90)	84	Unspecified	84	11	4	36
Zhang[347] (USA)	R	132	72	96	T1a	10			2.2
Epstein[348] (USA)	R	94	Died < 4 years (75 years) Survived 4 years (65 years)	120 (96–216)	A1 [T1,T2]	8		6	

[*] *Four patients were lost to follow-up.*
[†] *R, retrospective; P, prospective.*

TABLE 28 *Survival statistics following conservative management in localised prostate cancer*

Study	Country	No of patients	Clinical stage	Mean age at diagnosis (years)	Mean follow-up (years)	Observed survival (%)		Progression free survival (%)	
						5 years	10 years	5 years	10 years
Adolfsson[344]	Sweden	122	T1/T2	68	7.5	80	50		
Johansson[341]	Sweden	223	T0–T2	72	12.5	67	42	67	56
Studies of early detection									
Chisholm[351]	UK	107	T0/T1	73.5	1–12	60	35		

prostate cancer (through histological examination of tissue removed at TURP or *ad hoc* PSA testing) or for those detected during screening programmes.

Only one RCT has so far been completed and reported in the literature. The VACURG trial of radical prostatectomy versus placebo (i.e. conservative management) showed no difference in overall survival between the two groups,[267,268] although the small sample size meant the study lacked sufficient statistical power, particularly as 22% of the randomised patients were excluded from the final analysis.

A number of prospective[19,343,344] and retrospective[345–348] studies of conservative management have been carried out and reported, primarily in the USA and Scandinavia, with a small number in the UK. The majority of these studies have focused on patients with incidentally-found prostate cancer, with only two examining the effectiveness of conservative management in patients with early detected disease.[347,348] In addition, two papers report on a pooled analysis from six studies.[20,349]

The pooled analysis involved 828 case records from six observational studies published since 1985 of patients treated conservatively.[349] The results suggested that conservative management is a reasonable treatment option for men with grade 1 or 2 localised tumours, especially if their life expectancy is 10 years or less.[349] The authors indicate, however, that RCTs are required to compare conservative management with more aggressive treatment in men with such tumours, and that other strategies are required for men with higher grade disease.[349] In a follow-up paper, Chodak argues for patients to select their treatment based on the information available, indicating that watchful waiting is a valid option for all men.[20]

George and colleagues prospectively followed the natural history of localised prostate cancer in a series of 120 men in Manchester, England, for 7 years.[19] Thirteen further patients were omitted from the series because they received therapy immediately after a negative bone scan owing to clinical anxiety concerning either stage or grade of the tumour. Disease progressed enough to require treatment in 23 patients, of whom one man developed metastases and subsequently died. No details were reported on tumour grade at diagnosis. The majority of men died from causes other than prostate cancer. There is a tendency to include older (mean age = 75 years in study by George and colleagues) and less fit men in studies of conservative management, who are unsuitable for surgery and who subsequently die of diseases unrelated to the prostate.

Initially untreated prostate cancer has been followed up for 10 years in a population-based cohort of 223 men with early stage disease (T0–T2, M0).[343] Expectant management was the standard treatment in Sweden for localised (T0–T2) disease at the time that this study was conducted. Unfortunately, there were severe biases in the recruitment process, which included altering the recruitment criteria half way through the study. During the second half of the study, fewer patients with poorly differentiated tumours were included. At 10 years, 124 patients (56%) had died of all causes, 19 (8.5%) of prostate cancer. One further patient had died of prostate cancer without clinical evidence of disease progression prior to death. Disease progression occurred in 76 patients (34%), of whom 26 (12%) developed metastases. The authors reported a higher rate of disease progression during the first 5 years of follow-up, but this was probably due to the higher number of poorly differentiated tumours included early in the study. Age at diagnosis was not associated with disease progression or disease-specific death. Grade was a strong predictor of progression-free survival (see *Table 27*). The relative risk of dying of prostate cancer was 58.4 times higher in patients with poorly differentiated tumours than in those with well differentiated tumours.

A prospective surveillance study was performed in Sweden by Adolfsson, who followed a series of 122 patients with clinical stage T1–2 tumours, receiving no initial anti-tumour therapy, for 10 years.[344] Only men with well-or moderately well-differentiated tumours were included in this series. There was no statistical difference between T1 and T2 tumours in speed of progression to stage T3, and neither grade nor stage had any significant effect on metastatic progression.

There have been a number of retrospective, observational studies, the majority of which are American[346–348,350] with a small number of studies from the UK,[351] and Norway.[345]

Waaler and colleagues in Norway retrospectively followed a series of 94 patients with clinically-localised prostate cancer.[345] As with most of the retrospective observational studies, a combination of men with clinically diagnosed tumours and men with incidentally-detected tumours were included in the same series and analysed together, making specific conclusions difficult to draw.[350] In Waaler's series there was a statistically significant difference in progression-free survival between tumour stages, from 100% survival for T0 focal disease to 18% for T1–T2 disease, at 5 years ($p = 0.00005$). Tumour grade had a significant impact on mortality from prostate cancer; 2% of patients with G1 tumours, 17% with G2, and 25% with G3 tumours died from prostate cancer ($p = 0.01$).

Whitmore and colleagues in the USA retrospectively followed a series of men with stage B1 [T2a, T2b] tumours. As with previous findings, rates of disease progression increased with tumour stage.[346] There was wide variation in follow-up (24–298 months), but overall progression occurred in 65% of those with stage B1 [T2a, T2b] and 78% of those with B2 tumours. There was a much greater proportion of well-differentiated tumours in men with stage B1 [T2] disease than more advanced tumours. Conclusions from this study can only be tentative. It is unclear how patients in this study were selected, and with only the inclusion of stage B [T2] tumours wider conclusions cannot be drawn. Life table analyses were not performed.

Several of the retrospective series report high intercurrent death rates, which is related to the older men recruited into these series compared to those in series of radical prostatectomy or radiation treatment. Intercurrent death rates range from 20% to 47% in studies reporting patients' mean age as ranging from 67 years to 86 years.[343,345,346,348]

Although it is difficult to combine these various studies because of the wide range of potential biases caused by patient selection (for example, older and more unfit men being assigned to conservative management), the studies reach a number of findings. There is, for example, a relatively low prostate cancer-specific death rate for men receiving conservative management. In addition, the most important predictor of progression is tumour grade, with both local progression and the development of metastases strongly related to grade of tumour. The rates of local progression for confined disease range from 35% to 70%, and to metastases are from approximately 10% to 15%.

Conservative management following early detection of prostate cancer

A small number of studies have reported specifically on early detected tumours managed conservatively. In an American study, for example, Zhang and colleagues followed 132 patients with stage T1a prostate cancer for a median of 8 years.[347] Of these, 13 (10%) had either locally or systematically progressive disease after long-term follow-up. There was a wide interval from detection of the disease to progression, ranging from 6 months to 20 years (mean 7 years). Ten patients have been treated for prostate cancer and, at the last follow-up, no patient had died of the disease, although two had died of unrelated causes.[347]

Similarly, another American series of men with stage A1 [T1, T2] tumours, reported a low rate of progression – eight of 94 men (8.5%) – over a 10-year follow-up period.[348] It should be noted that this study by Epstein and colleagues was conducted prior to the introduction of PSA testing. Progression rates are reported to be higher in later studies where the detection of progression is higher. Contrary to previous findings neither volume nor grade were found to be predictive of progression.

Studies currently underway

An evaluation of the effectiveness of conservative management as a treatment for men with early localised prostate cancer currently has to rely on mainly observational evidence. To date, only one RCT has been published, and this has a number of flaws. There are, however, several RCTs currently underway, although the majority rely upon patients discovered incidentally with prostate cancer.

There is, for example, the MRC RCT comparing total prostatectomy, radiotherapy and conservative management (PRO6) for newly-diagnosed patients with T1 and T2 prostate cancer (for details see above, p.40).

The EORTC has two studies investigating immediate versus deferred treatment, one of which takes only patients with localised disease. In study 30891, patients who have localised disease but are deemed unfit for radical prostatectomy are randomised to receive either immediate or deferred therapy, orchidectomy or a luteinising hormone–releasing hormone (LH–RH) antagonist. In March 1994, 360 patients had been recruited; 750 patients are required for completion.[352]

The Danish Prostate Cancer Study Group (DAPROCA) is currently comparing a policy of no treatment with radical prostatectomy in patients with T2 disease. As yet there are no published results.

The PIVOT trial is currently underway in the USA but is experiencing recruitment problems. In this study, those randomised to conservative (expectant) management are not reviewed until the PSA level reaches 100 – a level which is unacceptable to many clinicians (for further details, see above, p.40).

Thus RCTs previously published and currently underway involving conservative management seem unlikely to provide evidence that will evaluate the effectiveness of radical versus conservative treatment for men with localised disease. What is required is an RCT of radical versus conservative management for localised prostate cancer detected early by PSA assay, DRE, TRUS and biopsy testing.

Conclusion

The natural history of prostate cancer is poorly understood (see Chapter 2), which makes the evaluation of conservative management difficult. In the past, the majority of studies examining outcome following conservative management have been conducted on men with clinically-discovered or incidentally-diagnosed disease following TURP, although increasingly men are being diagnosed earlier because of PSA testing.[210,342,353] Men detected through PSA testing tend to be younger, with more clearly localised disease, and many are likely to be considered suitable for radical treatment.

Although there is a lack of evidence from RCTs, it has been shown that conservative management is a treatment option for all men diagnosed with prostate cancer.[20] The majority of men diagnosed with prostate cancer will go on to die from other causes. The clearest predictor of outcome is, however, tumour grade. Men treated conservatively with higher grade disease are much more likely to progress locally or to metastases than men with low grade tumours. The lack of RCTs means, however, that it is not possible to determine accurately the costs and benefits from conservative management compared with more radical treatments.

As with the majority of treatment studies, there is little, if any, assessment of the quality of life of patients undergoing conservative management for prostate cancer, nor assessment of the acceptability of this approach. Little is known about how patients cope with their diagnosis and with the knowledge that they are receiving no active treatment. The adverse effects of deferring treatment may include patient anxiety resulting from knowing that cancer is present and that the opportunity for curative therapy may be lost by delaying definitive treatment. The current MRC trial is attempting prospectively to assess quality of life. In patients with low grade tumours the risk of progression and metastases has been reported to be less than 50%, but this still remains a significant concern.[21] Research is also warranted into the effect on clinicians of deferring treatment in men who may go on to die of the disease at a later date.

It would seem that the best option currently would be to present patients with information about each of the treatments and allow them to make the choices best suited to their own circumstances. In the meantime, the research community should prepare the way for an RCT of conservative management versus radical prostatectomy for men with PSA-detected prostate cancer.

Chapter 6

Economic evaluation

Economic evaluations, particularly of cost-effectiveness, combine information on cost with data concerning effectiveness, and are very sensitive to assumptions about effectiveness. For prostate cancer, evidence from adequately controlled studies concerning treatment effectiveness is so sparse and inconclusive that studies of cost-effectiveness are inevitably hampered. Thus studies attempting to evaluate cost-effectiveness of population-screening programmes have to rely heavily on assumptions about treatment which are poorly founded and can be biased. There is some literature concerning the economic appraisal of different treatment modalities for early localised prostate cancer, but the main concentration of the literature concerns the decision about whether or not to screen for prostate cancer. There is very little on the cost-effectiveness of diagnostic techniques, other than in the context of screening. The evidence that does exist provides no support for population screening, with results being particularly sensitive to assumptions about treatment effectiveness.

Introduction

In order to set this part of the review in context, it is worth considering one study of the costs associated with the treatment of prostate cancer at different periods of the illness. Taplin and colleagues[365] looked at costs of treatment for initial therapy, continuing therapy and terminal therapy, where initial therapy was defined as lasting up to 6 months after diagnosis, continuing therapy was defined as lasting from 6 months after diagnosis to 6 months before death, and terminal therapy was defined as the 6 months prior to death. Hospital and community costs incurred by 1849 individuals during 1990 and 1991 were included (valued in mid 1992 prices, US$). The average cost of initial care was found to be $9090, continuing care $1379 and terminal care $15,551. The impact of stage, age and co-morbidity on each of these costs was assessed. While the costs of terminal care did not differ with any of these factors, the costs of initial care decreased with increasing age (but did not vary with stage or co-morbidity), and the costs of continuing care differed with co-morbidity (but not with age or stage).

There are a number of difficulties in evaluating the relevance for the UK of the economic appraisals that have so far been conducted. First, the majority of studies have been conducted in the USA, and it is questionable how cost data from the USA should be interpreted in the light of the very different systems of health care. It is likely that the characteristics of patients vary between the two systems and also that the costs associated with different types of resource use are very different. Second, the studies tend to concentrate either on limited ranges of costs, or on a limited period. The studies looking at the costs of different treatment alternatives tend to be limited to the immediate hospital costs associated with particular alternatives, without necessarily considering the costs associated with treatment or follow-up after this initial period. Studies of the economics of screening are frequently limited to consideration only of the cost of a test.

Costs and benefits of treatment

A number of US studies have compared various aspects of the costs of alternative treatments in isolation from considerations of effectiveness. Hanks and Dunlap compared the costs of three treatments for early localised prostate cancer: lymph node dissection with iodine-125 implant, radical prostatectomy, and external beam radiation.[366] The study was observational, with large variations in the numbers of patients studied in each of the groups. The costs of immediate hospital treatment associated with lymph node dissection and radical prostatectomy were not dissimilar, with the mean cost of lymph node dissection with implant being $13,900 (n = 8) and that of radical prostatectomy being $14,100 (n = 12) (1984 prices, US$). The costs associated with external beam radiation were much lower, with a mean of $5500 (n = 128). There is some question as to whether the patients varied systematically in some manner that could have affected the costs of treatment.

These costs can, to some extent, be set alongside the results of a decision analysis which looked at the potential gain in quality-adjusted life-expectancy for three treatment strategies, two of which are similar to those costed above: radical prostatectomy; external-beam radiation; and watchful waiting (conservative management).[367] Fleming and colleagues based the parameters of their model on a review of the literature and were careful to ensure that estimates were favourable to the treatment alternatives rather than watchful waiting. They concluded that, although either treatment compared to watchful waiting provided some benefit in terms of life expectancy for all patients aged under 70 years, treatments were generally less beneficial in terms of quality-adjusted life-expectancy. If the most optimistic assumptions about treatment effectiveness are used, patients aged 60–65 years are shown to benefit from either of the treatments compared with watchful waiting. In most other cases, however, treatment offers less than a 1-year improvement in quality-adjusted life-expectancy or decreases quality-adjusted life-expectancy compared with watchful waiting. Generally, invasive treatment was found to be harmful for those aged over 70 years. The authors conclude that, in general, the potential benefits of therapy are so small that the choice of appropriate treatment will be sensitive to patient preferences for outcomes and discounting. Given the results obtained by these authors, it can be questioned whether the costs quoted by Hanks and Dunlap for radical prostatectomy and external beam radiotherapy[366] are worth incurring.

Further cost analyses have been concerned with other aspects of treatment including the means of lymph node dissection (laparoscopy or open),[368] the use of surveillance to detect recurrence,[370] and the length of stay following radical prostatectomy.[297] The US study of lymph node dissection found that the total in-patient costs associated with laparoscopy were higher whether or not positive or negative nodes were found. While open dissection incurred higher post-operative costs resulting from a longer length of stay, this post-operative cost was outweighed by the greater operative costs associated with laparoscopy. The authors of this study stated somewhat equivocally that, with more technical expertise, the cost of laparoscopy could be expected to fall but that more sophisticated equipment could also cause costs to rise.

The costs associated with PSA, bone scan, prostatic acid phosphatase and alkaline phosphatase as forms of surveillance to detect recurrence of prostate cancer were compared in the USA.[369] The authors concluded that the latter tests provide no clinically useful information beyond that provided by PSA and, given that they are costly, should be eliminated. The authors also compared the annual cost of a surveillance programme in which those with cancers graded as A, B or C would receive PSA tests, with one in which those with cancers graded A received a physical examination and history only, whilst those graded B or C also received PSA testing. For the former case, the annual cost in the USA was estimated at $268.3 million in the year 2000 (1992 prices, US$); for the latter, the estimate was $174.4 million.

A comparison of early discharge after radical prostatectomy with usual discharge showed a reduction in cost/case between 1989 and 1994.[297] There were, however, problems with the study in that the hospital's policy to promote early discharge was not separable from a general downward trend in the length of stay. The study also concentrated only on hospital costs, and did not estimate the impact on community costs.

It is clear from this discussion that the application of economic evaluation to the treatment of prostate cancer has been relatively limited. The number of applications of the techniques to the issue of prostate cancer screening has, however, been much greater. It should be stated here, however, that doubts about the cost-effectiveness of treatment for early localised cancer of the prostate must inevitably impact on the likely cost-effectiveness of screening.

Costs and benefits of screening

There are no estimates of the likely cost of a prostate cancer screening programme in the UK, but the cost to the health service of the first year of a national screening programme for those aged 50–74 years in the USA has been estimated as being between $5.2 billion and $14.1 billion,[370] with a further estimate that screening men aged 50–70 years would change the allocation of spending to this area from 0.06% of the total health care budget to more than 5%.[371] Against such levels of costs must be weighed the likely benefits associated with screening.

As with estimates of the cost-effectiveness of prostate cancer treatment, evaluations of the economics of screening for prostate cancer have had to work with the limited data available on all aspects of screening; in particular, the effectiveness of treatment and the sensitivity of diagnostic tests. Although a review of the whole area[151] has concluded that the most cost-effective approach to screening seems to be a combination of DRE and PSA for primary screening, with TRUS as a diagnostic tool for those with abnormal findings, there is a broader question concerning whether, given the expected costs and benefits, screening should be attempted at all.

Studies from the USA by Littrup and colleagues[372–376] have attempted to apply the approach of cost-benefit analysis to prostate cancer screening. The cost-benefit analysis approach is the only method of economic appraisal that is able to quantify whether or not a programme is worthwhile. This is because benefits are valued in monetary terms and, hence, are commensurate with cost.[377] The difficulty with applying this method is, of course, the problem of valuing health outcomes in monetary terms.

The studies by Littrup and colleagues have estimated the net benefit per individual screened for prostate cancer from the societal viewpoint. The benefits included were future medical savings from treating earlier cancer, reduced suffering from prevention of advanced disease, lost wages and the value of reassurance from a negative test. Costs included were the costs of the screening test, the cost of subsequent staging and treatment, the cost of adverse effects of screening tests and morbidities of therapy, and the psychic cost of false-positive test results.[372,373] No information is provided about the year of cost data, but the analysis is conducted in US$, with publications occurring mainly during 1993 and 1995.[372–375,378] Data on the probability of the main clinical events are drawn mainly from the ACS–NCDCP.[376] Many of the valuations of cost and benefit included in the equation are based on judgement but there is also extensive sensitivity analysis. This sensitivity analysis shows that the most important economic parameters are, first, the sensitivity of the screening test, second, the economic benefits from early therapy (which comprise the sum of future medical benefits, reduced suffering and lost wages resulting from the proportionate increase in earlier stage disease) and, third, disease prevalence.[373]

The analyses initially reported by the authors show net costs resulting from each of the different screening methods. These varied from $474 per individual screened using DRE alone (performed by a highly skilled examiner), to $5544 per individual screened using DRE plus PSA assay at 2 ng/ml.[372] (Assuming a drop in the ability of the practitioner performing DRE, however, results in a large change in the net cost of DRE, making this option one of the most costly.[372,376]) It is of interest, although unsurprising, that the authors found that greatest cancer yield occurs when all three tests are performed but that this option also resulted in the highest net cost per individual screened, $10,092.[376]

Later analyses look at the benefit per unit cost associated with screening particular groups,[375] and the use of a tailored biopsy approach.[374] A modified benefit-cost equation illustrates that if early detection is not deemed worthwhile in general, there is an underlying potential for economic gains to be made by discouraging participation by those at highest risk. This is likely, however, as the authors state, to be socially unacceptable.[375] Other modifications show that improving early detection efforts for African-American men (for whom there is higher incidence of the disease) leads to a smaller range of potential net benefit values, but these are still clustered around zero.[375] Assuming the use of a tailored biopsy (where this refers to biopsy of all patients with PSAD > 0.12 ng/ml/cc or with concurrently suspicious DRE/TRUS), the authors show, leads to lower net costs for the use of PSA assay and DRE compared with the use of a systematic biopsy.[374]

What is perhaps of most interest about these studies, however, is the fact that the authors do not explicitly accept the implication of their results, which suggest that screening for prostate cancer is not worthwhile. The studies consistently demonstrate net costs (i.e. negative benefits) from screening,[372–375] and, given that they have deliberately chosen the cost–benefit methodology, it is surprising that they do not pursue their results to the logical conclusion: since the benefits of screening are lower than the costs, programmes for prostate cancer screening should not be implemented.

The value of screening is also questioned in cost–utility analyses conducted by Krahn and colleagues and Cantor and colleagues.[379,380] Krahn and colleagues' analysis took the perspective of the third party payer, and estimated utilities from ten clinicians on the basis of study specific scenarios using the time trade-off approach. The analysis found that all programmes result in a net increase in cost compared to no screening, with cost-effectiveness ratios ranging from $113,000 to $729,000 per incremental life-year saved (1992, US$). Although screening with PSA assay alone appears to be the most attractive screening policy, **each** screening programme resulted in QALY loss (the gains in life expectancy and metastatic morbidity were outweighed in all cases by the short- and long-term effects of the therapy). Even within the sensitivity analysis, all bar one (the most optimistic) screening policy was dominated by no screening, with results being sensitive only to assumptions about the effectiveness of treatment. As with the other evaluations of prostate cancer screening, there are concerns about the low quality of evidence, but the study deliberately biases its results in favour of screening where there are questions about the quality of data inputs to the model.

Cantor and colleagues also developed a decision-analytic model, basing utilities on the preferences of ten male patients with no history of prostate disease and, again, using the time trade-off method).[380] The model evaluated annual screening (DRE, PSA assay initially, plus biopsy/TRUS and biopsy). The Markov model used found that there was a small gain in life expectancy as a result of screening (24.86 versus 24.22 years). Once quality of life was incorporated into the decision there was a fall in QALYs (24.14 versus 23.47). The authors concluded that the decision to screen is sensitive to changes in preferences regarding adverse effects of treatment, but concluded that where quality of life is considered important, annual screening should not be recommended.[380]

Costs of different screening options

Empirical and modelling studies have produced a number of estimates of the costs associated with various forms of screening for prostate cancer.[31,381–384] These are shown in *Tables 29* and *30,* with *Table 29* showing those studies which include the costs associated with screening, but not with subsequent treatment. *Table 30* shows those studies which have incorporated the cost of treatment in their estimates. One further study, not shown in the tables, has estimated that breast cancer screening is between 3.7 and 5.2 times more costly than screening for prostate cancer, but it is difficult to ascribe much importance to this result given that the costs included are only those of detecting the respective cancers.[385]

The most comprehensive of the studies shown in *Tables 29* and *30* is that by Gustafsson and colleagues,[382] which assessed, on the basis of an empirical study, the health service, patient and indirect costs of six screening strategies for men aged 55–70 years. Costs of subsequent treatment were not included. The total cost per thousand individuals screened, cost per cancer detected, cost per small (T2A or less) cancer detected, and cost per cancer treated was assessed for each of the screening strategies. The most costly option per thousand individuals was also the most effective – screening using all three strategies. In terms of cost/treated cancer, however, it also far exceeded the costs of other strategies (as with the work by Littrup and colleagues[376]), and the most cost-effective option in terms of cost per cancer treated was initial screening using PSA assay, with TRUS performed on all those for whom the PSA level was 4 ng/ml or above. The incremental costs* associated with successively more intensive screening strategies were compared with the baseline assumption that the most cost-effective strategy would be pursued. It was concluded that the incremental cost for performing DRE on all individuals rather than

TABLE 29 *Estimates of the cost of prostate cancer screening, where costs included are those associated with screening and biopsy, but not subsequent cancer treatment*

	Cost/ participant	Cost/cancer detected	Cost/early (small) cancer detected	Cost/cancer saved from becoming advanced
Abramson:[381] USA (1992, US$)				
DRE + TRUS	$231	$7240	–	–
Chadwick:[31] UK (1991†, £)				
PSA + TRUS if PSA > 4 ng/ml	£25	£1654	–	–
Gustafsson:[382] Sweden (1990, US$)				
DRE	$74*	$3100*	$12,420*	$4970*
TRUS	$98*	$2950*	$9750*	$4880*
DRE, TRUS, PSA + re-examination > 7 ng/ml	$161*	$4470*	$13,410*	$7000*
PSA + DRE if PSA > 4 ng/ml	$71*	$3560*	$17,800*	$5930*
PSA + TRUS if PSA > 4 ng/ml	$83*	$3180*	$13,770*	$4590*
DRE, PSA + TRUS if PSA > 4 ng/ml	$116*	$3630*	$12,900*	$5530*
Torp-Pedersen:[383] (1988, US$)				
DRE	–	$4108	$5869	$28,552
TRUS	–	$6250	$7671	$22,177

* *Includes estimates of indirect costs*
† *Paper does not provide information on the year for which prices are given, year of publication shown*

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* *The incremental cost quoted is the extra cost per extra cancer treated for cure, for successively more intensive screening programmes.*

TABLE 30 *Estimates of the cost of cancer screening programmes in which costs of subsequent treatment are included*

	Cost/ participant	Cost/cancer detected	Cost/early (small) cancer detected	Cost/cancer saved from becoming advanced
Abramson:[381] USA (1992, US$)				
DRE + TRUS	$520	$16,300		
Carlsson:[384] Sweden (1989, US$)				
No screening				$50,572[*]
DRE[†]				$20,086[*]
DRE+TRUS[†]				$16,224[*]
Quebec:[386] Canada (1994, Canadian $)				
PSA – initial screen	Can$138			
PSA – steady state	Can$77			

[*] *Includes estimates of indirect costs*
[†] *Screening every two years*

just those with PSA levels > 4 ng/ml was $1100, the incremental cost per cancer treated for cure for performing TRUS on all individuals with PSA levels > 4 ng/ml rather than DRE on all individuals was $2700 and the incremental cost of performing TRUS on all attendees rather than on just those with PSA levels > 4 ng/ml was $7450. Up to this point, this incremental cost approximates the cost of detection with the baseline option, indicating that it may be advantageous to choose one of these more effective strategies. More resource intensive options, however, have very much higher incremental costs.

Many of the other published cost analyses are limited in scope. Two of the studies described in *Tables 29* and *30* have not compared alternative means of screening (e.g. Chadwick and colleagues,[31] Abramson and colleagues[381]) and, therefore, provide only information of limited usefulness. Others have used a restricted notion of costs (e.g. Torp-Pedersen and colleagues' study estimates costs on the basis of user charges for diagnostic tests alone[383]).

Three analyses have attempted to combine information about the costs of screening with information about life expectancy.[39,371,386] A study conducted in Quebec looked at the diagnostic and treatment costs of screening men aged 50–69 years by PSA assay, and provided a best estimate of the cost-effectiveness ratio of $213,000/life year gained (1994 prices, Canadian $).[386] This was, however, stated to be based on 'insecure'data. An earlier study found a much lower cost per year of life saved – ranging between $2267 and $3687.[39] This study includes only the cost of tests (DRE) and biopsy, however, and is much older (1984 prices, US$) than the majority of other studies reviewed. A 1990 US study containing a comprehensive decision analysis found that any benefits of screening, in terms of fewer deaths from carcinoma (which, as it states, would be difficult to prove) would be reduced by significant treatment mortality (estimated at 100 times the treatment mortality without screening).[371] The paper also concluded that a screening programme for all men aged 50–70 years would be 'prohibitively expensive'.[371]

Conclusion

The economic evaluations discussed have been conducted mainly in the USA and Sweden. It is clear, however, that what evidence exists provides little support for population screening, with results being extremely sensitive to assumptions about treatment effectiveness. Data concerning treatment effectiveness in this area are poor and inconclusive. If screening is to occur, however, it is also clear that, although conducting all three diagnostic tests simultaneously is likely to be most effective, it is unlikely to be the most cost-effective alternative.[376,382] It is clear that the costs of introducing population screening in the UK would be prohibitive: extrapolating from estimates of cost for the first year of a national screening programme for prostate cancer in the USA,[370] UK costs would be of the order of £500 million to £1.5 billion.

Chapter 7

Screening

Screening for prostate cancer has recently received considerable attention in the medical literature and lay press in the UK. Observational studies suggest that DRE and PSA, combined with TRUS and biopsy where indicated, can detect organ-confined prostate cancer. A large number of concerns still exist, however, about whether population screening can currently be justified. In particular, there is little robust evidence concerning the effectiveness and acceptability of treatments for the disease. In addition, there is a lack of knowledge about the epidemiology and natural history of the disease. The potential costs of a screening programme are huge. Overall, the lack of good quality data on these major aspects means that screening for prostate cancer should not be introduced in the UK.

Introduction

The ultimate aim of screening is to reduce morbidity and mortality from a disease by detecting and treating it before symptoms appear. Screening for prostate cancer involves the examination of asymptomatic men, firstly by rectal palpation (DRE) and/or a PSA test (see Chapter 3). Men who are 'positive' (usually with a raised PSA level and/or asuspicious finding on DRE) are then investigated further. Further investigation can involve ultrasound (TRUS) and/or examination of suspicious lesions by biopsy, or random systematic biopsy. Those who are found to have the disease are then clinically staged and can be offered treatment, such as radical prostatectomy or radical radiotherapy (for confined disease), or can be monitored by watchful waiting until they develop symptoms which can be treated palliatively.[387]

The international perspective is somewhat mixed. Screening for prostatic cancer has, for example, been policy in Germany since 1978, and rectal examination is included in insurance-supported annual check-ups in Belgium. Some prostatic cancer screening has been introduced in parts of the USA. In France, work-site PSA screening has been launched by occupational health services for men between 50 and 65 years of age.[388] There is, however, no international consensus on the introduction of formal screening programmes. The International Union Against Cancer (UICC) declared in 1990 that screening for prostate cancer should not be recommended because of the likelihood of over-treatment.389 In addition, the US National Cancer Institute has stated that "there is insufficient evidence to establish that a decrease in mortality from prostate cancer occurs with screening by digital rectal examination, transrectal ultrasound, or serum markers including prostate specific antigen".[390]

However, guidelines advocating annual DRE and PSA testing for men over the age of 50 years have been published by the American Urological Association and the American Cancer Society. These have been implemented by many American urologists and so unsystematic screening is in effect in some parts of the USA.[391,392] In the UK, there is no formal screening programme, but there has been pressure from some quarters to introduce one.

Screening studies

A number of observational studies of various types of screening programmes have been undertaken, mainly in the USA, but also in other countries, including the UK. There are a number of causes of possible bias in these studies which mean that, although they provide some evidence on a number of screening issues, the results have to be interpreted with considerable caution. Many of these studies rely, for example, on volunteers willing to respond to invitations for screening, and few have assessed any selection biases which might result.

In addition, 'lead-time bias' and 'length time bias' may affect results.[393] Lead-time bias occurs when asymptomatic tumours are detected earlier by a screening test or programme but the earlier detection does not affect the course of the disease. Where lead-time bias occurs, it will always appear that the screened population will survive for longer and have a higher proportion of organ-confined disease because their tumours were discovered earlier than they would have been if they had become symptomatic. Length-time bias occurs because asymptomatic tumours detected through screening tend to grow more slowly than tumours that are symptomatic, and again the screened population will appear to survive longer and have more organ-confined disease. This will occur in the absence of any real improvement in mortality from the disease.

It is clear that both these potential kinds of bias are likely in the case of prostate cancer. Early detection does tend to detect small asymptomatic tumours, and it is well known that many men harbour small tumours which do not become clinically evident within their lifetime. The fact that many prostatic tumours are not life-threatening means that there is a high risk of over-treatment resulting from any screening programme. The relatively poor levels of accuracy of the major detection tools in this area also mean that high levels of over-diagnosis (particularly biopsies which are found to be negative) will also occur.

Details of published screening studies are given below. In addition, very many papers have been published which present opinions concerning screening for prostate cancer. A relatively small number present the case for[394,395] or against screening,[396–398] with the majority concluding that further research is required (particularly RCTs) before mass screening can be recommended.[7,18,117,370,387,394,398–403]

Randomised controlled trials

The ideal way to determine whether screening is beneficial is to conduct an RCT of screening but, as yet, no long-term multi-centre randomised trial of screening for prostate cancer has been published. Two trials are currently underway – one with centres in several countries in Europe (the European Randomised Study of Screening for Prostate Cancer – ERSPC) and the other in the USA.

Eight pilot studies for this trial have been conducted in Rotterdam and Antwerp.[404,405] The study endpoint is mortality from prostate cancer. There is no attempt to control treatment, although it is stated that radical prostatectomy is the preferred treatment for organ-confined disease.[404] Other major aims of the study are to evaluate the efficiency of screening tests, to predict life-years gained and calculate the costs of screening policies. Some 130,000 men aged 55–70 years are to be recruited from the general population and randomised to screening or no screening.[404] The aim is to use PSA assay, DRE and TRUS in the screening group, with all suspicious lesions biopsied, and random biopsies for men with a PSA level higher than 4 ng/ml. The general rescreening interval is 4 years, with the first follow-up at 10 years.[404]

Preliminary findings from the first year indicate that 26% of those invited agreed to be randomised. For these 1228 men, the adjusted detection rate for prostate cancer, based primarily on TRUS, was 3.3%.[404] Of the tumours detected in year one, 50% were confined to the prostate (T2). In the second year, a further 2163 agreed to be randomised and were tested for PSA as well as DRE; 8.6% had suspicious findings on DRE, 16.5% on TRUS and 2.8% had PSA levels > 10 ng/ml.[404] An adjusted detection rate of 2.8% was calculated.[404] In the third year, TRUS criteria were altered a little, resulting in an adjusted detection rate of 3.7%.[404]

A large number of men biopsied because of suspicion of cancer had negative results. In year one, only 26% of those biopsied had cancer, with 24% in year two, and 39% in year three, the latter as a result of greater accuracy from altered TRUS criteria.[404]

More up-to-date results from the ERSPC indicate that more than 10,000 men have now been randomised, with a cancer detection rate of 4.3% (Schröder, presentation at British Prostate Group conference, York, 1996). Final results of the trial will not, however, be available for approximately 10 years.

The National Cancer Institute in the USA is conducting a multicentre RCT of screening for cancer at four organ sites, including the prostate (the PLCO trial).[406,407] Each individual will be screened for several cancers at one visit and will be followed for a minimum of 10 years. A total of 74,000 men aged 60–74 years at entry are being randomised into two study arms, half to undergo annual cancer screening and half to continue their normal health care routine. The occurrence of disease-specific morbidity and mortality will be determined and compared between the two groups. For prostatic cancer screening, PSA and DRE tests are being assessed. At present the pilot phase of the project is underway.[408]

The major methodological problem with these trials is that the groups in which the cancer has been detected, clinicians have been permitted to offer patients a choice of treatment, resulting in wide variations and patient selection. Unless these treatments are very well documented, a screening **and treatment** programme will not be able to be specified. Raised public consciousness about prostate cancer may also encourage many trial participants to be screened even if they are randomised to the control group.[409] Unfortunately, final results of these studies will not be available for some time.

Other observational screening studies

A number of other studies of screening for prostate cancer have been conducted (see *Table 31*). Detection rates vary widely, from 0.2% to 5.6%, although the most commonly attained figure is approximately 3%. Several difficulties arise in interpreting these studies. They vary according to the screening methods used, age of participants, sample sizes, methods of obtaining the samples, and cut-off points employed to determine further tests. Each of these factors can introduce its own effect on the detection rate and so results from all the studies need to be interpreted with caution. The majority of studies rely upon volunteers, often recruited following response to advertising, and so the relevance to the general population is questionable.

***TABLE 31** Screening studies, with detection rates by various modalities*

Study	Country	Number screened	Age range screened	Method of screening	% biopsied	% with prostate cancer
Schröder[404]	Belgium	1228	55–70	DRE, TRUS		3.3
Schröder[404]	Belgium	2163	55–70	DRE, PSA		2.8
Mettlin[25]	USA	2425	55 >	PSA, DRE		2.4
Chadwick[31]	UK	472	55–69	PSA, DRE	6.1	1.7
Kirby[410]	UK	568	55–70	PSA, DRE		2.0
Chodak[398]	USA	811	45 >	DRE		1.4
Catalona[34]	USA	1653	49 >	PSA	6.7	2.2
Catalona[109]	USA	10,251	50 >	PSA, DRE, TRUS		3.0 initial 2.0 serial
Abramson[381]	USA	564	40 >	DRE, PSA		3.0
Chodak[83]	USA	2131	45–80	DRE	6.7	1.7
Dillman[50]	USA	579	39–84	DRE, PSA		3.5
Moon[414]	USA	414	40–59	DRE, PSA		1.2
Imai[84]	Japan	5770	60 >	DRE		1.0
Waaler[85]	Norway	480	45–67	DRE	3.3	0.2
Varenhorst[86]	Sweden	1494	50–69	DRE		1.1
Perrin[411]	France	863 370 GP		PSA DRE		0.3 1.6
Pode[412]	Israel	1000	50–75	PSA, DRE		3.1
Gustafsson[73]	Sweden	1782	55–70	PSA, DRE, TRUS	21	3.6
Imai[364]	Japan	3526	> 40	PSA, DRE, TRUS	9	1.4
Smith[35]	USA	24,346	> 49	PSA		4.8
Deliviolotis[147]	Greece	1400	> 50	PSA	3.4	1.6
Labrie[149]	Canada	1002	45–80	PSA, DRE, TRUS		5.6
Bangma[37]	Netherlands	812	55–77	PSA, DRE, TRUS	9.1	2.0
Brawer[99]	USA	701	> 50	PSA	11.6	1.9
Mettlin[102]	USA	2999	55–70	PSA, DRE, TRUS		5.2
Pedersen[87]	Sweden	1163	50–69	DRE	4	1.1
Catalona[32]	USA	6630	> 49	PSA, DRE	17.6	3.9
Lee[368]	USA	784	60–86	PSA, DRE	9.8	2.8

A small number of general conclusions can be reached. The use of a combination of PSA testing and DRE appears to be the most efficient method of first line screening, although it still creates a large number of false positives. Repeated (serial) screening appears to result in more cases being detected than a one-off programme.

The majority of studies have been carried out in the USA, although there have been studies in Japan and various countries in Europe (see *Table 31*). Two studies have been undertaken in the UK, both based in primary care but linked to a specialist urology department, and these are described in some detail below.

A pilot study of screening for prostate cancer, based on a single general practice in the UK was published in 1991.[31] Of the 815 men who were invited to attend for a health check, 472 (58%) agreed to be screened using PSA assay and DRE, followed by TRUS and biopsy if indicated.[31] Seven prostate cancers were detected (1.7%), all of them confined to the gland.[31]

Kirby and colleagues in the UK reported the first year results of their pilot evaluation of a GP-based screening programme.[410] Of the 856 men invited to attend for a health check, 568 (66%) accepted. PSA tests and DREs were performed and men with abnormalities underwent TRUS and biopsy where indicated. The overall detection rate for the screened population was 2%.[410] Eleven tumours were detected in total, but only six of these were confined to the prostate and three had metastases.[410] Thus screening had only detected tumours early enough for potentially curative treatment in half of those identified. At least three tumours (stage T1) were missed but subsequently detected following TURP. In all three of these cases, the PSA value lay between 4 and 10 ng/ml. In using a PSA cut-off level of 4 ng/ml in this study, without DRE, the false positive rate was 12%; when acting on a positive DRE as well, this rate fell to 1%.

A small number of studies were undertaken examining the usefulness of DRE alone as a screening tool.[82,84–87] Samples of the population were drawn from various employment schemes,[82,85] following advertisement,[82,86] or those attending urology clinics[84] in the USA,[82] Japan,[84] Norway,[85] and Sweden.[86] On the whole, these studies detected a smaller number of prostate tumours than PSA tests alone or combined with DRE and TRUS (see *Table 31*), and most authors considered that screening with DRE alone was not sustainable.

The remaining studies used a combination of PSA testing and DRE in the first instance, usually supplemented by TRUS and biopsy for suspicious lesions.

The most influential work has come from Catalona and colleagues who have carried out a number of studies on an increasingly large scale. In one study, 1653 ambulatory men responded to a press release asking for healthy men to participate in a study of screening using the PSA test, and 37 cancers were detected (2.2%).[34]

In an update of this study, Catalona and colleagues reported on 10,251 men aged 50 years and over who presented to a prostate cancer screening programme.[109] PSA level was measured first. For those whose initial levels were less than 4 ng/ml, the test was repeated 6-monthly; for any man with a level above 4 ng/ml a further PSA sample was taken and, if the level was confirmed, DRE and TRUS were undertaken, followed by biopsy where indicated.[109] The rate of detection was 3% from the initial PSA measurement, and 2% from the serial measurements.[109]

In a further update, the clinical and pathological nature of the 1169 tumours detected were examined.[35] Some 97% had clinically-localised tumours (T1 or T2), of which 39% were not palpable.[35] Serial screening resulted in a higher proportion of pathologically organ confined disease than initial screening and, although this finding was not statistically significant ($p = 0.2$), the authors speculated that it would become so with longer periods of serial screening.[35] In addition, serial screening may be preferable because of the various factors causing temporary elevations in PSA (see above, pp.13–14).

In the ACS–NPCDP study (described above, Chapter 3, p.12), 2425 healthy volunteer men were examined.[25] Of these, 16.3% were recommended for biopsy, and 52 cancers were detected – an overall rate of 2.4% (1.3% of those men aged 55–60 years, and 3.3% of those over 65 years).[25] The authors admitted that the findings provided little insight into the cost-effectiveness of screening for prostate cancer.[25] They also indicated that the men included in the study were volunteers and, thus, a self-selected group.

In a follow-up paper, results were given for 156 cases of prostate cancer detected out of the total study group of 2999.[102] Of these, 83 cases were detected at the first examination (2.8%), with 38 in the second year, 13 in the third, 18 in the fourth and four after 5 years.[102] The majority of tumours were organ-confined although, following surgery, 36% were upstaged.[102]

In other studies, samples of the population were derived from a local health check,[411] following advertisement,[50,381] random selection,[412] or those attending GP or urology clinics[411] in the USA,[83,381,413] France,[411] and Israel.[412]

Two other studies tackled the issue slightly differently. In a study of younger men, 414 men aged 40–59 years were evaluated by DRE, PSA assay and a questionnaire.[414] Five cancers were detected (1.2%), with none in men between 40 and 50 years.[414] The authors concluded that PSA testing had some utility in detecting prostate cancer in younger men, but that it was not able to detect cancers early enough for potentially curative treatment (two of the five were Stage C [T3]).[414]

One study has examined the characteristics of men who did or did not participate in a screening programme in the USA.[415] Unfortunately, participation required paying for the test and so, inevitably, those with a higher income were more likely to participate. The authors also found that non-participants were more likely to be very old or very young but that there was no difference in the occurrence of clinical prostate cancer between participants and non-participants – 1.7% in both groups.[415]

A small number of retrospective studies on screening have been carried out. A case-control study of DRE screening in the USA, for example, reported no statistically significant effect of routine screening with DRE on the prevention of metastatic prostate cancer. Cases (139 men with prostate cancer) were retrospectively identified from the case notes of those subscribing to a medical care programme. Method of diagnosis differed between cases, with some men presenting to a urology service with symptoms. Only 70% were technically ‘screened’ prior to symptoms. Each case was matched with one control, and a retrospective analysis of case notes revealed that the number of rectal examinations performed varied widely between the time of first examination and diagnosis of prostate cancer.[416]

A nested case-control study, based on stored serum samples collected from 49,261 men from four cohorts of healthy men, examined the ability of PSA testing to discriminate between men with and without prostate cancer.[148] The PSA results of 265 men who developed prostate cancer were compared with 1055 controls matched for age, study centre and duration of storage of sample. The PSA level was significantly higher in men with prostate cancer, with the sensitivity calculated at 81% (95% CI 54–96%).[148] The false-positive rate was 0.5%, and the authors claimed that PSA is a good enough screening test to justify a randomised controlled trial.[148] However, it was shown that the false-positive rate rises with increasing age, and issues of patient selection were not considered.

Several retrospective surveys on clinicians’ views on screening, for example, have been conducted. A study of Australian GP views on screening showed that many were uncertain about the screening tests available, some thought they should screen but few did so consistently.[417] A similar study carried out in the USA showed that there appeared to be a lack of information on cancer screening among these practitioners.[418]

Screening in high risk men

A clear elevated risk for prostate cancer has been found for men with first degree relatives with prostatic or breast cancer (see Chapter 2). Screening first degree relatives of prostate cancer patients is an option, and it has been shown to result in a high rate of detection of clinically-relevant cancers. In one US study, 24% of the high risk men screened had tumours without having experienced symptoms. However, pathological staging revealed that 50% of the tumours were locally advanced, one with seminal vesicle invasion.[231] As this was a prospective study designed to assess this issue, and not a screening programme in progress, it is unclear whether earlier screening would have detected the tumours at a curable stage. It is likely that some urologists in the UK currently screen relatives of patients. Further studies are required to assess the effectiveness and acceptability of such schemes.

Conclusion

Studies suggest that a combination of PSA and DRE testing is more effective than either modality alone for the detection of localised prostate cancer. Both DRE and PSA assay used alone can detect tumours, but each would miss a number of cancers that can be detected using both tests together. A number of studies suggest that a detection rate for prostate cancer of between 2% and 4% is realistic for screening programmes. The accuracy of the tests is not particularly high for screening, leading to large numbers of men proceeding to biopsy but found to be negative. In addition, although it has also been shown that the tests identify localised tumours, perhaps 50% are upstaged following surgery.

Thus, although there have been a number of studies examining screening for prostate cancer, their observational designs and variable selection methods mean that any conclusions must be treated with caution.

Evaluation of screening

A number of criteria are commonly used to determine the suitability of a condition for population screening for disease. These rely on evidence concerning a range of epidemiological and health service factors,[419–421] including the following.

- Epidemiology (the burden of suffering should be sufficiently widespread in the population to warrant screening).
- Natural history (the natural history of the condition, including development from latent to declared disease should be adequately understood).
- Treatment (there should be accepted efficacious treatment(s) for patients with recognised disease).
- Resources and services (facilities should be available for the definitive diagnosis and treatment of those found to be positive).
- Diagnostic tests (there should be a suitable test or examination for diagnosis and screening which must be simple, easy, non-invasive and cost-effective).
- Acceptability of test (the test should be acceptable to the population).
- Case selection (there should be an agreed policy on whom to treat as patients).
- Costs (the cost of finding and treating cases should be acceptable to society).

Each of these factors will be considered below, drawing upon the evidence reviewed in this document.

Epidemiology

The epidemiology section (see Chapter 2) has demonstrated that prostate cancer is an important public health problem. In UK men, it is the second most common cause of death from cancer. With an increasing life expectancy, improvements in diagnostic techniques, and a rise in public knowledge and demand for testing, the prevalence of the disease is increasing.

Proponents of screening for prostate cancer believe that early detection and radical treatment of organ-confined disease would reduce or even reverse this increasing prevalence. Post-mortem/autopsy studies indicate that incidental histological evidence of prostate cancer is very high and consistent across the world. Only a small proportion of these actually become clinically evident, however, with many more men found **with** prostate cancer than dying **of** it. Screening would inevitably identify many men with cancer who would probably not benefit from treatment. It is unclear whether screening would be followed by a reduction in morbidity and mortality from the disease.

Natural history

The natural history of invasive breast cancers detected by screening is well known, and it is assumed that the majority would progress to clinical disease if left untreated.[396] In contrast, the natural history of prostate cancer is poorly understood (see above pp.3–4). Asymptomatic forms of the tumour which never prove fatal are common in men over the age of 60 years. Even in the fatal forms of the disease, many men remain asymptomatic until the late stages of the disease.[391] Many cases of prostate cancer are discovered incidentally following assessment or surgery for lower urinary tract symptoms or bladder outlet obstruction.

It would appear that the severity of prostate cancer ranges from non-fatal slow-growing tumours which remain asymptomatic and probably require no treatment, to aggressive fast-growing tumours which metastasise quickly, often before symptoms are noticed. In between are those cancers that are confined to the prostate in the early stages and it is these that screening seeks to identify.

There is, however, some doubt as to whether screening would be effective in detecting sufficient tumours early enough in their natural history to alter the current level of mortality from the disease, particularly as it is not possible to predict which microscopic lesions will develop into malignancies.

Diagnostic tests

Diagnostic screening tests need to be simple to perform, relatively inexpensive, and provide accurate information about the presence or absence of the disease if the screening programme is to be feasible. Three screening tests have been proposed for prostate cancer: DRE, PSA and TRUS, with biopsy being used to confirm the diagnosis.

These screening tests satisfy some but not all of these criteria. The ‘front-line’ screening tests (DRE and PSA) and are relatively easy to perform and relatively inexpensive. The true sensitivity and specificity of these tests is hampered by the lack of knowledge concerning the natural history of the disease, making the determination of false positives and negatives difficult to assess. Studies have shown widely fluctuating rates for these tests, but it would appear that PSA measurement in addition to DRE, followed by TRUS for suspicious lesions, is the most accurate method for detecting prostate cancer through screening, with biopsy reserved for the investigation of suspicious lesions.

The interval between screening tests is an issue which requires careful evaluation. Most of the studies above relate to one-off testing, although if a screening programme were introduced, screening would have to occur at intervals. Catalona's work has indicated that serial screening (annually) improves the detection rates of prostate cancer.[109] An analysis of the rate of interval cancers diagnosed between 3-yearly screening mammography was carried out in the north western region of the UK. The incidence of interval cancers in the third year after breast screening approaches that which would have been expected in the absence of screening and suggests that the 3-year interval between screening is too long.[422] Insufficient knowledge about the natural history of prostate cancer and the lack of RCTs involving serial screening precludes the determination of the optimum interval between screening tests at the moment.

It remains that a large-scale RCT of these screening tests is required to evaluate their cost-effectiveness in detecting potentially treatable cancers.

Acceptability of tests

In order for screening to have a chance of success, the initial diagnostic tests need to be simple, non-invasive, and acceptable to both the population to be tested and the clinicians performing the tests. In the first stage of screening for prostate cancer, these tests would involve the taking of a blood sample and a DRE. It is generally assumed that these are acceptable to most patients and clinicians, although little work has been published. A pilot of the screening trial being undertaken in Antwerp, Belgium, showed that 23% reported that the DRE had been painful, with 55% reporting some discomfort.[117] However, 95% of the men participating in the first round of screening were willing to be rescreened in the following 2 years.[117]

Several studies have been conducted looking at the psychological distress caused by breast screening (reviewed in Lidbrink[423]) as well as other types of screening.[424] These have shown that the effects on the individual and, at times, on other family members, even after cancer has been excluded, can be very great. It has been claimed that "even with the assumption that screening can save lives, the net effect of mass breast cancer screening is questionable and appears to be rather detrimental".[425] One published study has looked specifically at the psychological effects of a screening programme for prostate cancer, and found that the invitation and attendance for screening *per se* created some stress which disappeared after 2 weeks regardless of outcome.[426] In a further study of 1494 men in Sweden, randomly selected to participate in a screening programme of DRE and biopsy, 17% felt distress during the initial examination and 57% of those biopsied experienced anxiety.[87]

Small pilot studies of screening in the UK, particularly breast screening, have shown that many patients agree to attend without foreseeing possible physical morbidity from diagnostic tests or treatment. They also tend to fail to consider possible psychological harms from false-positive results, being unnecessarily labelled as having cancer, and having to make decisions about treatment.[424,427]

Further evaluation is required relating to quality of life in screened and non-screened men with prostate cancer to assess the social and psychological effects of the screening procedures and the additional years of knowledge of diagnosis. In addition, the spouses of these men may also undergo considerable stress.

Treatment

There are three main treatments for localised prostate cancer: radical prostatectomy, radiotherapy, and conservative management (close monitoring, with active treatment for symptoms if they develop). Each of these involves its own risks. The active treatments can involve iatrogenic effects, including pain, hospitalisation, incontinence, impotence, and occasionally, death (see Chapter 5). In some cases, when the treated cancer would not have caused morbidity or mortality, the patient may experience harmful side-effects without the possibility of benefit.[428] With conservative management, the patient is at risk of progression which, in a small number of cases, may be fatal.

The question remains as to whether early detection of prostate tumours can enhance life expectancy and the quality of that life. The aim of screening is to detect confined tumours that can be removed, thus effecting a cure. Clearly, current modes of screening are able to detect some such tumours but they also lead to the detection of untreatable or non-fatal tumours, as well as an unknown number of undetected tumours. Thus far, no adequate RCTs assessing the effectiveness and cost-effectiveness of treatments have been published. There are some data to suggest that radical treatment of organ-confined cancer can lead to long-term survival (see Chapter 5), but without confirmatory evidence from RCTs, such data cannot be relied upon.

In addition to the lack of good quality evidence on survival following radical treatment, very little research has been conducted on short- or medium-term outcome. Radical treatment can clearly lead to a number of complications, some of which are likely to have a severe impact upon quality of life. Research into these aspects, preferably within the context of an RCT is sorely needed.

In the absence of evidence concerning outcome and effectiveness, a large question remains over the ethics of allowing screening or even a randomised screening study. Without basic information concerning short, medium and long term treatment outcome, men should not be subjected to screening tests which will inevitably lead to unproven radical treatment in those with screen-detected disease.

Ethical issues

General guidelines under the Declaration of Helsinki declare that the overriding principle must be that concern for the individual must prevail over the interests of science and society.[396] Screening programmes involve introducing an intervention into a healthy population via screening tests. In screening, it is generally acknowledged that a stronger promise of benefit is required than in the treatment of sick people.[396] The debate about the ethics of screening for prostate cancer tends to form a continuum. At one end lies the argument that the benefit in terms of lives saved from a screening programme for prostate cancer can overcome concerns about the potential harms involved in screening large numbers of healthy men. The alternative view is that a trial of screen-ing is not ethical currently because of the lack of evidence concerning the benefits from early treatment. Many researchers and clinicians remain in the middle ground.

Resources and services

Currently, there is no national screening service for prostate cancer in the UK, although there are increasing concerns about *ad hoc* screening by GPs due to patient-led demand for PSA testing. Aside from the issues surrounding the effectiveness of PSA testing as a screening modality, increased PSA testing is resulting in increasing referrals to already hard-pressed urology clinics. If, as seems likely, such ad hoc screening increases further, some urology units will find it difficult to treat new cases quickly, causing some anxiety. It is clear that UK urology services do not currently have the facilities to cope with population or even targeted screening. In the UK, long waiting times for an appointment to a urology out-patient clinic are common even without the pressures of screening.[429]

If screening were to be introduced, substantial investment in diagnostic and treatment facilities would be required to manage the large numbers of men who would require investigation. In addition, decisions would have to be made regarding the management and delivery of the service, and the roles of primary care and specialist urological services.

Costs

The economic implications of setting up and maintaining a prostate cancer screening service remain to be properly evaluated. The funding of such a service would be considerable. Additional costs would be incurred by the setting up of quality assurance schemes to maintain standardised levels of PSA measurement. Serum samples would need to be frozen quickly to ensure accurate measurements, and the practicalities and costs would need to be addressed.

A Swedish breast screening study has shown that the costs of following-up women with false positive results were almost one-third of the total cost of screening all women.[423] It is likely that the costs of following-up false positives in a prostate screening programme would also be considerable, both in financial terms and because of the anxiety that would inevitably occur.

The little evidence that has so far been collected in Sweden and the USA from uncontrolled studies suggests that a screening programme for prostate cancer would be prohibitively expensive.

Conclusion

"It is an unfortunate fact that many questions relating to the planning and development of screening services during the last 20 years have been based on little more than a confrontation between enthusiasts and sceptics."[430]

Increased public awareness of screening programmes (cervical and breast) and the availability of the PSA test have contributed to an increase in informal screening for prostate cancer in the UK. Most health authorities and GPs feel this is on the increase, and there are fears that demand may lead to the introduction of screening programmes without appropriate investigations of the effectiveness and cost-effectiveness of such a service.

In the UK, lessons should be learned from the introduction of breast and cervical screening. In particular, these include the consequences of the high rates of false-positive results, anxiety caused, and additional, often unnecessary, investigative and treatment procedures undergone. Within the breast-screening literature, no trial has shown an overall benefit of mammography for women under the age of 50 years, although this procedure is still advocated for women below this age.[431]

It is clear from the section above (pp.70–72) that many of the criteria for assessing the need for a population screening programme have not been met for prostate cancer. Considerable concerns about the potential value of such a programme arise from the lack of knowledge about the epidemiology and natural history of the disease, and the poor levels of accuracy inherent in the screening tests. Even more serious is the paucity of good quality evidence concerning the effectiveness and cost-effectiveness of treatments for localised disease, particularly the lack of RCTs in this area. The absence of such data, combined with the possible costs of a screening programme, can only lead to a conclusion that population-based screening for prostate cancer should not be introduced.

Chapter 8

Recommendations

Clinical practice

Diagnosis

- In order to establish a definite diagnosis of prostate cancer, several diagnostic techniques are required in sequence. The most common 'first-line' techniques are DRE and PSA testing, with TRUS and biopsy being reserved for secondary investigation and confirmation.

- DRE is relatively quick and easy to perform, but there are concerns about its accuracy and performance. DRE misses approximately 20% of cancers which can be identified by PSA measurements but are not palpable. Nearly 30% of cancers found where PSA values are within the normal range are, however, detectable by DRE. DRE thus remains an important diagnostic tool.

- The use of PSA testing for all men attending urology clinics cannot be recommended because the comparative effectiveness of treatment options for localised prostate cancer is not known. PSA testing should be limited to men with clinical evidence of prostate cancer who have a life expectancy of at least 10 years, and only following full counselling about the implications and uncertainties of treatment.

- Measurement of serum PSA is recommended in the follow-up of men with known prostate cancer to monitor tumour progression.

- TRUS has a number of uses: to estimate the size of the prostate, guide needle biopsies, diagnose prostate cancer, stage tumours, and to monitor disease progression.

- The use of DRE, PSA or TRUS alone cannot be recommended.

- TRUS-guided biopsy is generally considered to be the 'gold standard' for the diagnosis of localised prostate cancer. It is not, however, completely accurate, and a number of complications can occur. There is evidence to suggest that random systematic biopsies can identify additional tumours, although these tend to be small and in the earliest stages of development.

Staging

- The 'gold standard' for staging of localised disease is surgery, including lymphadenectomy.

- Clinical staging techniques, such as DRE, PSA testing and TRUS are unreliable, with approximately one-half of patients found during surgery to have higher stage disease than these techniques suggested clinically.

- After initial promise, imaging techniques including MRI and CT scanning have not proved to be particularly useful in staging.

- Bone scanning is recommended for assessing metastatic spread in patients with extra-capsular disease or high PSA levels. There is no evidence to suggest that it should be used more widely.

Treatment

- Evidence concerning the effectiveness and cost-effectiveness of treatments for localised prostate cancer is poor and inconclusive.

- Rates of radical prostatectomy and radiotherapy are increasing in the UK, particularly for younger and fitter men with localised disease. Comparative evidence is poor, but it is suggested that cancer-specific survival rates are approximately 80% following conservative management, 90% following radical prostatectomy, and 60% following radical radiotherapy. These data relate to highly selective observational studies, yet still only find a 10% difference between radical and conservative treatment. In addition, short and medium term outcomes, particularly morbidity and quality of life following treatment, have not been properly addressed.

- Conservative management is a reasonable treatment option for men with localised disease.

- In the absence of evidence from RCTs concerning the relative benefits of treatments, informed patient choice should be a major consideration.

- The level of uncertainty and paucity of research evidence suggests that radical treatments (radiotherapy and prostatectomy) should not be performed without the accompanying collection of pre-operative and follow-up data, and a co-ordinated programme of audit.

Screening

- There is no justification for the routine use of PSA testing in primary care. GPs should be actively discouraged from using PSA tests for the purposes of early detection.

- Younger men with a strong family history form a distinct group and such men may warrant a selective approach to PSA testing and DRE, although such men should be fully counselled as to the uncertainties of treatment effectiveness for localised disease.

- Although prostate cancer is a serious public health problem, it appears to have a long natural history and it is impossible on current evidence to identify the tumours that will progress to be life-threatening.

- DRE and PSA testing, combined with TRUS and biopsy where indicated, can detect localised prostate cancer in approximately 3–5% of men aged over 50 years, depending on the criteria employed and the use of the tests cross-sectionally or serially. There is little evidence concerning the acceptability of these tests to the general population.

- Major questions remain concerning the efficacy and effectiveness of treatments and until these are resolved there is no justification for the introduction of a screening programme.

- The potential costs of a screening programme are huge, and the limited economic evaluations available provide little support for screening.

Research

Epidemiology

- Information about the natural history of prostate cancer is required, particularly to identify tumours which will progress to become life-threatening.

- Further evidence concerning the discrepancy between trends in incidence and mortality is needed.

- More precise information about aetiology and risk factors is required, particularly genetic risk.

Diagnosis

- Definition of the optimum method of diagnosis is needed.

- Further understanding of the biomolecular and physiological properties of PSA is required, alone and in combination with other modalities.

- Definition of the most clinically useful form of reporting PSA levels is required, whether by age, density, velocity or molecular form.

- Information on the acceptability to patients of each of the diagnostic techniques is required.

- Further assessment is needed of the reliability of TRUS in the UK, particularly inter- and intra-observer variation.

- Investigation of the consequences of increasing numbers of biopsies is required, particularly tumour seeding and infectious complications, including the value of prophylaxis.

- Examination of the types of tumours detected using random biopsy techniques and the relationship between detection rate and PSA level is needed.

Staging

- Improving staging performance is a high research priority.

- Pursuit of molecular markers of likely progression is required.

- The prognostic value of bone, CT and MRI scanning in the UK requires investigation.

- Investigation of the natural history of prostatic tumours is needed, particularly T1 and T2.

- Examination of the effectiveness of laparoscopic compared with pelvic lymphadenectomy is required, including an assessment of any complications arising.

- Further investigation into the value of DNA ploidy is required.

Treatment

- A large-scale, randomised, controlled trial comparing radical prostatectomy with conservative management for men with localised prostate cancer is urgently required to assess the comparative effectiveness and cost-effectiveness of these treatments. Such a trial should measure a range of short and medium term outcomes in addition to mortality and progression.

- Detailed investigation of short and medium term outcomes is required for each of the major treatment modalities, particularly identifying treatment complications and effects upon quality of life, including sexual functioning and family life.

- Further evidence is required concerning the optimum approach for radical prostatectomy.

- Further examination is needed of the significance of PSA levels in detecting progression following radical treatment.

- The optimum programme of conservative management needs investigation. The content of conservative management programmes needs to be made explicit and described fully to enable this treatment modality to be investigated thoroughly. Issues which need to be addressed include the level or rate of change of PSA required before intervention, and the type of intervention used (TURP or hormonal therapy, for example).

- In-depth assessment of men's perceptions of the acceptability of conservative management as a treatment option is required, particularly in view of increased public awareness of the disease.

- Comparative effectiveness of different forms of radiotherapy requires investigation (external beam, conformal and seed implants, for example).

- Standardisation of treatment complications to be measured in all studies is required, including clear definitions of types of incontinence and the introduction of patient-completed instruments for this purpose (such as the ICS*male* questionnaire[432]).

Economic evaluation

- A full economic evaluation of the cost-effectiveness of the major treatment options is urgently required, particularly set within the context of a large randomised controlled trial.

- Studies including UK costs are required.

- Costs of various forms of surveillance for recurrence in the UK are needed, particularly in comparison with PSA testing.

Screening

- If data became available suggesting that radical treatments were effective and cost-effective, then it would become necessary to mount a full evaluation of the effectiveness and cost-effectiveness of screening versus no screening in the general population. Such a study, which would necessarily have to follow on from a randomised, controlled trial of treatment, would need to be on a large scale and involve the randomisation of men to screening or no screening, with outcome in terms of mortality assessed 10–15 years later.

- The current practice in some urology centres to screen men with a strong family history of prostate and/or breast cancer and to treat them radically should be evaluated through audit or research.

When (and if) evidence becomes available that suggests that radical treatment is effective, then the following research on screening might be required.

- Economic evaluation of the cost-effectiveness of various screening options, applied either to the general population or specific target groups, such as those with a family history of prostate or breast cancer, set within a randomised controlled trial.

- In-depth assessment of men's perceptions of the acceptability of conservative management as a treatment option within a screening programme, particularly in view of increased public awareness of the disease and the perceived possibility of cure.

- While DRE and PSA can be used as 'first line' screening tests and are relatively simple to perform, there has been insufficient investigation of the psychosocial implications of widespread availability of such tests.

- A full investigation of the most suitable method of counselling for men entering screening should be carried out.

- A full review of facilities and personnel required for screening will be needed, including the provision of special clinics and additional resources for treatment.

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Appendix

Search strategies, selection and assessment of studies

Search strategies

A wide variety of bibliographic sources were consulted in order to identify the studies used in this review. Separate searches were performed for each of the major sections in this report. This resulted in duplication between references found because of overlapping subject-matter, for example epidemiology/risk factors/natural history, and diagnostic techniques/screening.

The major database used was Embase because of its European bias, supported by CancerLit to identify references originating from Medline and other sources. A systematic comparison of the relative coverage of Medline and Embase was conducted on a sample of articles. Other sources consulted were: Social Science Citation Index, Science Citation Index, PsycLit, DHSS-Data, Applied Social Sciences Indexes and Abstracts (ASSIA).

All-language searches were performed for 1990–95 for the major treatment and diagnosis searches. Economic evaluations were sought back to 1986 because of their relative scarcity.

Search terms: appropriate terms were identified by conducting trial searches in the databases and inspecting the thesaurus/keyword terms used to index articles deemed to be relevant. These were then applied in the full search procedure. For example, for the searches for studies of therapy, ‘prostate cancer’ (explosion search) was combined with various individual therapy terms such as ‘radiotherapy’ and ‘prostatectomy’. For diagnostic techniques the main subject term was combined with technique-specific terms including ‘echography’, ‘examination’, ‘diagnostic accuracy’, ‘PSA’, ‘biopsy’ and ‘magnetic resonance imaging’. For economic evaluations, 13 separate cost-related terms were combined with prostate cancer. Text searches (i.e. of title/keywords/abstracts) were used to complement index term searching in order to improve coverage.

A citation search was conducted on the early treatment trials of the US VACURG team, for cross-checking purposes. Some 600 references citing these studies were found.

Review articles and other reviews were identified through the bibliographic searches and through the NHS Centre for Reviews and Dissemination database. Citations from major review articles were utilised.

Unpublished information on current projects was identified through the NHS Projects Register, its USA equivalent HSRProj and through personal contacts/networks of this project’s staff and expert steering group. Some centres were contacted direct, such as the Agency for Health Care Policy and Research in the USA.

We had access to a Medline search on PSA covering 1991–94 (387 references).

The expert steering group was asked to identify key studies to include in this report.

The Director of the publishing house of the Chinese Medical Association was written to in an attempt to access research from China, as recommended in the *British Medical Journal* in 1994, but no reply was received.

In all, over 2000 references plus abstracts were retrieved and scanned for relevance.

Selection

Of the 2000+ references/abstracts obtained, 877 full-text items were retrieved and entered in to the project database. Of these, 432 have been included in the final report, following application of selection criteria.

Selection criteria were developed jointly by three members of the project team (SS, JD, AF) on a sample of references (the great majority including abstracts) for each major sub-topic of the review. These were then applied by the project researcher to the remaining items, with reference to the other team members in cases of doubt.

Primary selection criteria included: focus on early localised prostate cancer; study group size > 50, preferably > 100; primary research data included in report; because of the lack of experimental study designs in this area, the type of evidence included retrospective series as well as higher level studies; outcome data as appropriate to diagnostic or detection techniques, or therapeutic interventions. The criteria were applied loosely in order not to exclude studies of at least some value.

Assessment of studies

Key data items for tabulation for each sub-topic of the review were decided jointly. The studies selected for inclusion in the review were assessed and data extracted primarily by the project researcher with support from other team members (JD – epidemiology and screening; AF – PSA studies; JC assessed the economic evaluations).

The project researcher received advice and guidance on study appraisal from colleagues with expertise in epidemiological study evaluation. Therapeutic studies and economic evaluations were assessed using proformas (see below). The project researcher's therapeutic study evaluations were supported by a blinded, second opinion using the same proforma (AF) on a sub-sample of studies (1/8). Disagreements were discussed. Therapy studies were scored 0–2 on nine criteria and an overall score 0–2 also given. This was not based on a numerical summary of the item scores, since a low single item score (such as study group selection bias) could weight (negatively) the value of the whole study.

The possibility of important publication bias in the studies reviewed here is not strong. The lack of randomised controlled trials means that the use of funnel plots based on meta-analysis to give a statistical indication of publication bias is not possible. In the published studies of both diagnostic techniques and of therapies there is a certain amount of over-positive interpretation of results, especially in favour of interventionist approaches, in Discussion and Conclusion sections of papers, but the wide range of actual performance results reported suggests that bias toward publication of positive results is insubstantial.

Revision of drafts of this report involved a second, independent reading and assessment of many of the included studies. This was performed primarily by JD.

Study assessment forms

The form used to evaluate non-RCT studies of treatment comprised nine points:

- Recruitment/study group bias?
- Control/comparison group?
- Intended outcome measures?
- Appropriate outcomes measured?
- Outcome assessment blind?
- Do results meet study objectives?
- Statistical tests applied?
- All patients entered in study accounted for at conclusion?
- Centre/practitioner/experience bias?

The form elicited a 0–2 score and optional comments for each item, and overall for the paper.

The form used to evaluate studies in economic evaluation incorporated nine criteria as well as recording the type of study (cost of illness, cost-effectiveness analysis, etc.), inclusion of empirical data, therapeutic area, country, and year of cost data. The criteria were:

- Viewpoint (society, NHS, etc.)
- Source of data on probability of main clinical events
- Type of resource use identified
- Method of measurement of resource use
- Method of valuation of resource use
- Type of benefits measured
- Method of valuation of benefits
- Discounting applied and its rate
- Sensitivity analysis used and variables employed.

A 0–2 score was given for each item. Key results were noted separately.

Acute Sector Panel

Chair: Professor John Farndon, University of Bristol †

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Professor Kenneth Taylor, Hammersmith Hospital, London †

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Dr Keith Jones, Medicines Control Agency
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