How are we looking after prostate cancer?

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Introduction

The most recent statistics available show that in 1998, 216,000 people were registered as having cancer. In males, the most common tumour was lung cancer: 19,487 (18.3%) were registered, while prostate cancer came a narrow second, with 19,335 registrations (18.1%). Lung cancer deaths are declining, but there were 3370 deaths from prostate cancer in 1964, and mortality rates have nearly trebled since that time. The major increases in mortality rates were in the 1960s, 70s and 80s. However, in the late 90s, death rates appear to have plateaued.1,2

Are prostate cancer deaths increasing?

Is this increase in mortality rates real, a function of misdiagnosis, or the result of increased population numbers and later age of death? It is unlikely that clinicians failed to diagnose prostate cancer in the 1960s, as prostate cancer is relatively easily defined as a cause of death. The increase is not due to changing population numbers, because if we factor in population numbers, we see the same increase in mortality rates were in the 1960s, 70s and 80s. However, in the late 90s, death rates appear to have plateaued.1,2

Risk factors

Do we have any clues as to the reasons for the increased risk of death from prostate cancer? There is little evidence that there is an inherited basis to prostate cancer. In the Laval University study of 7277 men with prostate cancer, just 159 had a family history. The increased risk for a man with an affected brother is 2.6, and for an affected father, 1.2.5 Genetic change is widely reported in prostate cancer specimens. The most common abnormality is loss of heterozygosity. A very wide number of changes are seen, the most important being in chromosome 10p.6 It is possible that prostate cancer is a multi-step process where at least seven chromosomal changes are implicated, but it is not clear whether this process is primary and causal, as it may be in colorectal cancer, or an epiphenomenon.

It is likely that there are dietary causes for prostate cancer, with great changes noted in the epidemiology of the disease in migrating populations (who change their diet but not their genetic stock). The best evidence for a dietary basis to the development of prostate cancer comes from a prospective study based in The Netherlands of 56,279 men. During a median 6.8 year follow-up, 642 men developed prostate cancer, with cured meat and milk products found to be significant risk factors.
factors for the development of this disease. An enormous public health initiative to follow on the Government’s fruit initiative may thus be required if mortality statistics for this tumour are to be improved.

**Treatment of localized prostate cancer**

Prostate cancer can be considered to be three ‘diseases’. In a significant proportion of men, prostate cancer is indolent and causes no problem: foci of this class of prostate cancer are observed post mortem in the prostates of men dying from other causes. It is likely that these foci, which have parallels in the normal breast, thyroid and many other tissues, are innocuous.

**Surgery**

The second type of prostate malignancy is localized prostate cancer of small bulk, and there is considerable controversy over the management of this condition. The management of such ‘patients’ includes surgery, radiotherapy and active observation, where men are followed without therapy, and treatment given on symptom progression. For many surgeons, the criteria for operability include PSA levels <10–12 ng/ml and age <70 years. This defines a group of patients with a high chance for survival. We continue to have difficulty in assessing the value of surgery. There are currently only two published trials that compare surgery with any other management approach. One study involved just 96 patients and compared surgery to radiotherapy. The second trial of 695 patients compared surgery to watchful waiting, with 31 deaths in untreated patients and 16 deaths from prostate cancer in the surgery group. The largest surgical series come from the US, and are single-institution-based retrospective analyses. In one typical analysis of 2758 men, 10-year survival for well and moderately differentiated tumours was 80–94%, and for poorly differentiated tumours, 77%. It is argued that case selection leads to a bias in result reporting, because only patients with excellent performance status, who by definition do better, go to surgery.

In the Western world, the numbers of patients undergoing radical prostatectomy is dramatically changing, with operative rates increasing three-fold in the last decade. Careful analyses of clinical practice show that there are problems with this approach. For example, the series published by the major UK protagonists for surgery describes extension beyond the operative specimen in nearly 50% of the patients, indicating that the chance of a surgical cure was zero in this group. Post-operative complications include loss of potency in up to 70% of patients and 6% with late incontinence. This study was published in 1996, and it may be that current practice has improved, with a decrease in the proportion of patients with complications from surgery.

**External beam radiotherapy**

Patients with small-bulk prostate cancer can also be treated with radiotherapy. Single-institution figures for survival after radiotherapy indicate a poorer chance of 10-year survival for patients with poorly differentiated tumours than would be achieved by surgery, with figures ranging from 15 to 30% at 10 years. But it is argued that the survival of those patients with well and moderately differentiated small-bowel prostate cancer is equivalent. Radiotherapy causes complications, with loss of potency in up to 60% of patients and bowel and bladder toxicities in between 4 and 20% of patients. These are significant issues affecting life quality in the elderly.

It is hoped that the refinement of radiotherapy that comes from computer planning with delivery of conformal treatment will limit the toxicity to bowel and bladder. In recent times, there has been additional hope that there will be further benefits from radiotherapy with the use of concomitant anti-androgen therapy. There have been 14 retrospective and six prospective studies of anti-androgen therapy in combination with radiation for the treatment of localized prostate cancer. In these studies, anti-androgen treatment was given for different periods ranging from 3 months to lifetime use. Virtually all showed an improvement in local control of prostate cancer, that is in freedom from prostatic relapse. However, only two studies showed a survival advantage, one for patients with poorly differentiated tumours only. So, with this minimal evidence base and a knowledge of the side effects of anti-androgen use, which are osteoporosis, further loss of libido, anaemia and neurological dysfunction, the advantage of adjuvant hormonal therapy given for substantial periods may not be significant, although short-term treatment is to be recommended.

**Brachytherapy**

Brachytherapy has attracted a lot of media attention and patient interest. This is because of the ‘high tech’ nature of this approach, which gives hope of
an advance. There have been no randomized trials investigating the value of brachytherapy as a treatment for prostate cancer. In all, there are probably 15 brachytherapy published trials. Claims have been made that brachytherapy is likely to lead to an improvement in the control of the disease in comparison to external beam radiotherapy, but the jury remains out on this issue. While the jury remains out, we have to consider life quality issues, which remain significant, with sexual dysfunction and incontinence occurring with a similar frequency after brachytherapy as after radiotherapy and surgery. Further refinements of radiation by intensity modulation are thought to represent a way forward, allowing higher dosages of radiation to be delivered to the prostate with the potential for an increased chance of possible cure. Logically this cannot be the case and practically, it is not.

Active observation

Active observation offers an effective management policy without side-effects, and with this approach 87% of 828 men with well and moderately differentiated tumours survived 10 years, as compared with 34% with poorly differentiated tumours. The comparison of treatment options that describes the largest number of patients surveyed involved a retrospective analysis of Cancer Registry data involving 59,876 men. Ten-year prostate cancer specific survival is shown in Table 1.

In the UK, the Department of Health, through the NHS R&D programme, have funded a randomized trial comparing monitoring, surgery and radiotherapy involving nine clinical centres and 13,000 patients. The results will be available in 10 years. Meanwhile what is the patient to do? In our view, patients need to make informed changes based on an analysis of treatment outcomes and side-effects.

Screening

Prostate cancer can be detected by screening or diagnosed as a result of the development of symptoms. In this country, just 1% of the male population are screened, and this compares to about 68% of the male population in the US. Screening by PSA testing and digital rectal examination is of remarkably low specificity. A doubling of PSA levels beyond the normal range results in a chance of diagnosing prostate cancer of just 25%, and demand from men for screening is low. Nonetheless, it appears logical to the public that a test for cancer should lead to its diagnosis and there has been pressure to make this generally available. The Government has responded to public pressure. Until 1997, it was official policy not to recommend PSA testing. The NHS Cancer Plan published in 2000 changed this and, despite the lack of specificity, GPs have been instructed to offer a PSA test to men who are concerned that they may have prostate cancer—but only if the GP feels that it is appropriate to do the test and after offering information regarding the value of this test.

Hormonal therapy for metastatic and locally advanced disease

The major cause of death from prostate cancer remains metastatic disease and not localized tumours. How is this managed? Patients are treated by anti-androgen therapy and in this country, 60% of patients are treated by urologists without oncological follow-up; however, we are beginning to see changes in patterns of care as a result of central imperatives towards multidisciplinary management of cancer patients. The main controversy in this area concerns the value of anti-androgen therapy given as a combination treatment, i.e. treatment with an LHRH agonist with an additional anti-androgen such as flutamide or bicalutamide. Virtually all the prospective studies comparing single with combination therapies have shown a 7-month survival advantage to combination treatment. However, a large meta-analysis reported a 3% advantage to combination therapy with flutamide at 5 years, without commenting on the median survival of the patient groups. In our view, combination therapy is the treatment of first choice in this disease, as the meta-analysis seems to have missed the point.

Table 1  Ten-year survival in prostate cancer

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<thead>
<tr>
<th>Management...</th>
<th>Surgery</th>
<th>Radiotherapy</th>
<th>Conservative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade I</td>
<td>94% (91–95)</td>
<td>90% (87–92)</td>
<td>93% (91–94)</td>
</tr>
<tr>
<td>Grade II</td>
<td>87% (85–89)</td>
<td>76% (72–79)</td>
<td>77% (74–80)</td>
</tr>
<tr>
<td>Grade III</td>
<td>67% (62–71)</td>
<td>53% (47–58)</td>
<td>45% (40–51)</td>
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Data are survival rates (95% CI), taken from reference 22.
Prostate cancer survival

In 1998 the results of cancer survival throughout Europe were published, and for prostate cancer, as for many tumours, we were in the bottom four of the EC survival figures, with 44% survival at 5 years. It is good to know that in prostate cancer there has been an improvement, with 5-year survival increasing to 59.8% for patients diagnosed between 1993 and 1994, and followed-up to 31 December 2000.28 But, as with all announcements, when one looks a little more closely at the reasons for this and increased diagnosis of indolent, screen-detected cancer is factored in, the figures may not be as attractive as they first appear.

Prostate cancer research initiatives

Despite the negative press that the Government seems to be achieving in virtually every arena, in the controversial area of prostate cancer, they seem to deserve plaudits. In the financial year 1996, the total amount of money spent from central sources on prostate cancer research was £47 000. As a result of lobbying, an increase is projected to £4.3m for the financial year 2003–4, achieving some sort of parity with breast cancer. But this will not in itself get us to the distant goal of a cure for prostate cancer.

Hope, in embryonic form, may lie in the NCRI, a national centre for clinical cancer research, which some of us hope will form the basis for a National Cancer Institute. The point has been made that just £350m per annum is spent from all sources on cancer research in this country and this, at £5 per head of population per year, reflects very poorly upon our national status as the fourth biggest economy.29 The situation in cancer research is different in many European countries and in the US, where $4.2bn was apportioned to cancer research by the Senate Apportionment Committee, who gave where $4.2bn was apportioned to cancer research.

References


