Management of carcinoma of the prostate

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Every year in the UK nearly 10 000 men die from advanced prostate cancer. On average these individuals lose 9 years of their anticipated lifespan. The cumulative loss of expected life years therefore amounts to around 90 000 per annum, and many hundreds of thousands more retirement years are blighted or lost worldwide as a consequence of this very prevalent neoplasm.

Prostate cancer is a slow and insidious disease. In its early stages it is silent; symptoms only develop when the disease is either locally advanced within the pelvis, or after metastases have occurred. By this time the prospects of cure are remote, and treatment can only delay the relentless progress of the tumour. For this reason there have been many calls for early detection programmes designed to detect these prostatic cancers at an earlier, and hopefully curable stage. This clamour has been resisted in the UK on two grounds:

1. The concern about overdiagnosis and overtreatment of 'latent' tumours never destined to result in 'clinical' disease
2. The lack of evidence from randomized controlled trials that prostate-specific antigen (PSA) screening reduces prostate cancer mortality.

Set against this stance, however, is the mounting evidence that PSA testing does indeed detect clinically significant disease, and that in the USA, where early detection is extensively used, the mortality from prostate cancer has recently fallen by around 7%. As a consequence many informed men are now requesting both a PSA test and a digital rectal examination as part of their annual 'well man' check up. This in turn has resulted in a downward shift in the stage of prostate cancer seen at the time of presentation in those men tested.

STAGING THE DISEASE

The management and prognosis of prostate cancer depends critically on its stage at the time of diagnosis: early cancers can be cured, advanced tumours can only be palliated. Unfortunately the accuracy with which local staging can be achieved is still suboptimal. By contrast, distant metastases can be readily identified (Kirby, 1998). Men suspected of prostate cancer should undergo digital rectal examination (DRE) and PSA determination. Induration of the gland or a PSA above the usual cutpoint of 4.0 ng/ml is usually regarded as an indication for transrectal ultrasound (TRUS)-guided sextant biopsy (*Figure 1*) (provided the individual concerned has a life expectancy of more than 10 years and is therefore likely to benefit from curative therapy).

The presence of adenocarcinoma in one or more biopsy cores confirms the presence of local disease and prompts investigation to exclude or confirm the presence of metastases. Neither computed tomography nor magnetic resonance imaging scanning are very accurate in identifying local spread, which is often microscopic, but a radionuclide bone scan is a

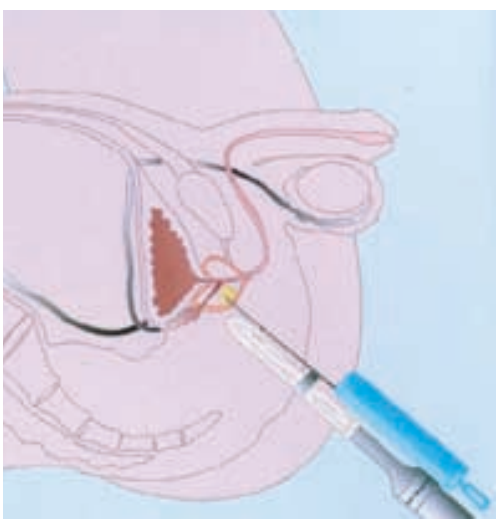

Figure 1. Transrectal ultrasound guided biopsy of the prostate.

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reasonably sensitive and specific test for bone metastases (Kirby, 1997) (*Figure 2*). Recently Partin et al (1997) combined the clinical stage, the PSA value and the Gleason score (i.e. the degree of differentiation seen on biopsy) to improve the accuracy of pretreatment staging (Gleason, 1992). These so-called Partin tables have been found to be useful in advising patients about the probability of extraprostatic extension and therefore the advisability of various treatment options for clinically localized disease.

MANAGEMENT OPTIONS FOR LOCALIZED DISEASE

For patients with biopsy-proven prostate cancer, there are currently four recognized treatment options (Kirby, 1998), as described below.

Watchful waiting

Because prostate cancer is generally a slow-growing tumour, predominantly affecting men beyond middle age, there has been a tradition of watchful waiting, or as some prefer to call it, 'deferred therapy' in the UK. For men with a life expectancy of less than 10 years, as a result of age or comorbidity, such an approach is reasonable. For younger men, however, deferring therapy until symptoms occur risks allowing the window of curability to close. If bone or other metastases become apparent during observation the patient could legitimately criticize the doctor for denying him the opportunity for cure.

In the pre-PSA era the concept of simply monitoring disease progress and treating symptoms as and when they occurred had greater appeal than it does today. However, in patients with low-volume, well-differentiated tumours diagnosed at transrectal resection, and those who are very elderly and/or infirm, watchful waiting still has an important role to play (Johansson et al, 1997).

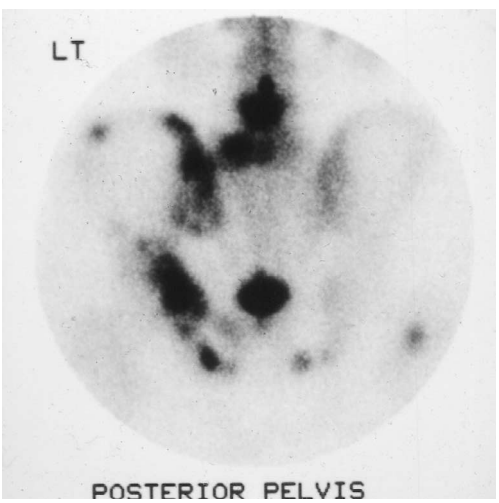

Figure 2. A radionuclide bone scan showing multiple metastatic deposits (hot spots) from prostate cancer.

Radical prostatectomy

Radical prostatectomy still has the reputation of being a difficult and dangerous procedure. In fact it can be reliably performed in less than 2 hours with an average blood loss of only around 500 cc. Provided the procedure is confined to younger men (<70 years), the mortality is well below 1% and the risk of serious incontinence less than 3% in experienced hands. The incidence of erectile dysfunction can also be minimized by judicious sparing of one or both neurovascular bundles, which pass posterolateral to the prostate to supply the corpora cavernosa of the penis.

Although the pathologist reports positive surgical margins in up to 30% of cases, many of these individuals never in fact suffer subsequent PSA progression and overall more than 70% of men are cured by this form of surgery. Because the PSA falls to <0.1 ng/ml after radical prostatectomy, follow up becomes straightforward and any subsequent PSA elevation is usually regarded as an indication for further therapy. Currently it is unclear as yet whether adjuvant radiotherapy or treatment with antiandrogen improves the outcome of patients with positive surgical margins after radical prostatectomy.

External beam radiotherapy

External beam radiotherapy (EBRT) still constitutes the most frequently utilized form of therapy for men with clinically localized prostate cancer in the UK. It carries the advantage of being outpatient based and being applicable to both localized and locally advanced cases. Its disadvantages include its failure to achieve 100% tumour cell kill in a significant proportion of cases, and the retention of the prostate with its unstable epithelium (almost all radical prostatectomy specimens reveal the presence of multifocal cancers and the associated premalignant changes of prostatic intraepithelial neoplasia).

A further problem occurs during follow up in that the PSA, although generally suppressed below 4 ng/ml, never reaches a nadir of <0.1 ng/ml and consequently leaves the clinician and patient in doubt as to whether biopsy of the prostate is needed to detect or exclude recurrent/residual disease.

Using traditional approaches positive biopsy rates exceeded 50% 1 year after EBRT. In order to improve the rate of 100% tumour kill two modifications of therapy have recently been introduced in the UK and elsewhere:

- The conformal targeting of radiation dosage
- The use of androgen ablation for 3 months pretherapy to downsize the tumour within the gland.

There is evidence to suggest that both these innovations have improved efficacy of EBRT and also reduced the complication rates (Dearnaley et al, 1999). The most troublesome side-effect of radiotherapy for prostate cancer is rectal radiation injury. This can result in tenesmus, diarrhoea and rectal bleeding, which may be long term and is often difficult to treat effectively.

Brachytherapy

Brachytherapy, using implanted radioactive iodine seeds, has been tried before for prostate cancer and abandoned because of lack of efficacy. Originally, however, the seeds were implanted at open operation. Modern brachytherapy uses a transperineal approach for either iodine-131 or palladium-103 seed implantation and TRUS guidance to ensure even seed distribution and urethral sparing. Although the centre that originated the technique has reported good results at 10 years (Ragde et al, 1998), it remains to be seen whether other institutions can match these results (remember Sir William Osler's adage: 'all new treatments work wonders for a while').

A recent sobering report from Massachusetts (D'Amico et al, 1998) found that brachytherapy only performed as well as radical prostatectomy and EBRT in patients with low-volume, well-differentiated cancers (i.e. low-risk patients). In those with more aggressive tumours brachytherapy appeared three times more likely to fail in terms of risk of a rising PSA after initial therapy.

MANAGEMENT STRATEGIES FOR LOCALLY ADVANCED DISEASE

Because PSA screening is not widely practised in the UK many patients still present with locally advanced disease (i.e. cancer that has spread beyond the prostate but not yet involved either regional lymph nodes or the skeleton). For these patients radical prostatectomy is not usually considered to be a viable option because the incidence of positive surgical margins and subsequent PSA failure is unacceptably high.

In younger, fitter men the best treatment usually involves EBRT preceded by 3 months tumour downsizing with a luteinizing hormone-releasing hormone (LHRH) analogue in combination with an antiandrogen (either bicalutamide or flutamide). Since the publication of a paper by Bolla et al (1997), many clinicians are now advising the continuation of androgen ablation therapy for a further 24 months because of the documented survival advantage of combined therapy over EBRT alone.

For older, less fit men, and those in whom radiotherapy alone is contraindicated (for example, as a result of diverticular disease or ulcerative colitis), hormone ablation therapy alone produces a good response that is well sustained and is less demanding on the patient. Recent data suggest that androgen ablation can be achieved as effectively in locally advanced disease with antiandrogen monotherapy alone, as with the combination of an LHRH analogue and an antiandrogen, with the added benefit of preservation of sexual function — an important quality of life determinant even in older men.

MANAGEMENT OF METASTATIC DISEASE

As a result of rising awareness of prostate cancer the number of new cases with metastases present at the time of diagnosis now appears to be falling. However, there are still substantial numbers of men who are seen for the first time with a PSA level that is markedly elevated (>20 ng/ml) and whose bone scan is positive when they first present, often with symptoms of low backache.

What treatment should be offered to these men? Currently patients should be advised that there is evidence to support immediate initiation of treatment rather than a strategy of deferred therapy. In a Medical Research Council study of nearly 1000 patients, those treated immediately had significantly less morbidity in terms of devastating complications of malignancy such as spinal cord compression and a small survival advantage (Kirk, 1997). Moreover, a proportion of those allocated to the deferred treatment arm died without hormonal therapy being utilized at all. This sad fact highlights the difficulties of achieving an adequate follow-up and monitoring of this often aged and infirm group of men.

If treatment is to be offered to these patients, which one offers optimum results? Currently there are no data to suggest that bilateral

orchidectomy produces a better outcome than medical therapy using LHRH analogues, usually used in combination for the first 6–8 weeks with an antiandrogen such as bicalutamide. Patients should therefore be offered the choice; experience shows that most will opt for medical therapy rather than surgical castration.

Data are conflicting over the advantage, if any, of continuing the antiandrogen in the longer term with the LHRH analogue as maximum androgen blockade to counteract the impact of the adrenal androgens (Crawford et al, 1989). Most urologists are only employing this strategy in younger men with low metastatic burden and good performance status. Another current idea in vogue is that intermittent hormone ablation therapy might offer some advantage in terms of reduced side-effects and greater efficacy. Several randomized studies are testing this hypothesis at present.

A particular group of younger patients with metastatic prostate cancer express the desire to preserve sexual function. For these men there is now evidence to support the use of antiandrogen monotherapy with bicalutamide. The results are almost equivalent to the use of LHRH analogues, but potency and libido are much less impaired.

MANAGEMENT OF HORMONE-ESCAPED PROSTATE CANCER

Currently the question of what advice to offer those patients who have received hormone therapy but whose PSA has started to rise again is one of the most vexed in uro-oncology. Here again there has been a move away from the therapeutic nihilism that prevailed until recently. Patients with cancer need a straw to cling to, and either stopping antiandrogens in those receiving maximal androgen blockade or antiandrogen monotherapy, or initiating antiandrogens in those who have received bilateral orchidectomy or monotherapy with LHRH analogues, can result in a temporary PSA and clinical response.

Other strategies include use of stilboestrol in combination with aspirin, or judicious use of chemotherapeutic agents (Amato et al, 1999). Many other approaches, including tyrosine kinase inhibitors, various immunotherapies and gene therapy, are currently being evaluated.

CONCLUSION

Attitudes are at last changing with regard to the management of men with prostate cancer. A more active approach has replaced the previously held laissez-faire view that the many men beyond middle age with this disease should simply be left in peace with their disease. Men in their 60s, 70s and even 80s are not content simply to give up and die from prostate cancer. We owe it to them to initiate and complete the studies to confirm the value of early detection and also identify and develop optimum treatment strategies in this insidious disease that afflicts so many men and their families. HM

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KEY POINTS

- Prostate cancer results in almost 10 000 deaths annually in the UK.
- Early detection strategies may be reducing mortality in the USA but have not been proven to be effective in randomized trials.
- Treatment options for localized cancer include watchful waiting, radiotherapy and radical prostatectomy.
- For advanced disease, androgen ablation is the mainstay of therapy.
- New approaches to the management of hormone-escaped prostate cancer a are being developed.