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FIGURE 1
Surgery with the assistance of the da Vinci robot which allows 3D visualisation and 10 times magnification

How should prostate cancer be diagnosed?

GPS ARE INCREASINGLY BECOMING INVOLVED IN THE CARE OF PATIENTS WITH PROSTATE CANCER.

Prostate cancer is currently diagnosed in more than 34,000 men every year. It claims more than 10,000 lives per annum in the UK, and many more than that internationally. Men dying from advanced disease often suffer intractable bone pain and debilitating lower urinary tract symptoms which have a considerable impact on their quality of life.

In the absence of a breakthrough in the treatment of metastatic disease, earlier diagnosis and more effective eradication of clinically significant disease currently seem to afford the best opportunity of stemming the tide.

How can high risk men be identified?

SCREENING

PSA

Recently, prostate specific antigen (PSA) population screening has been evaluated in two major randomised, controlled studies. The European Randomised Study of Prostate Cancer Screening (ERSPC) reported a 20% reduction in the risk of prostate cancer death with screening.[1] A subsequent reanalysis showed an even greater reduction in mortality (31%) when adjustment was made for contamination (men who had a PSA test while in the control arm) and non-attendance (men who did not take up the screening invitation). By contrast, the US-based Prostate, Lung, Colorectal and Ovarian (PLCO) screening study showed no significant difference in prostate cancer mortality between the two groups.[3]

The latter study was, however, flawed by the inclusion of almost 50% of individuals in the control 'unscreened' group who had in fact been tested for PSA values outside the study. This is a reflection of the pre-existing high level of public awareness of prostate cancer screening by PSA in the United States.

Even though the more mature European study confirmed that PSA screening is capable of reducing prostate cancer mortality, anxieties still persist, particularly surrounding the issue of overdiagnosis of clinically insignificant cancer, which may never be destined to result in morbidity or mortality.

PCA3

The above-mentioned limitations of the PSA test as a screening tool has driven research into other potential »

What are the evidence-based treatments?

Table 1

Risk evaluation in localised prostate cancer

Lower risk
PSA < 10 ng/ml
Gleason score 6 or less
Small proportion of biopsy cores infiltrated with cancer
Higher risk
PSA 10 ng/ml or greater
Gleason score 7 or higher
Greater proportion of biopsy cores infiltrated with cancer

biomarkers for screening for prostate cancer.[4] The PCA3 test, which is based on the analysis of a urine sample taken immediately after prostatic massage, looks promising in terms of sensitivity and specificity, and may also preferentially identify less well differentiated, higher risk cancers, rather than those which are clinically insignificant.[5] More clinical trials are required to increase the evidence base surrounding this marker, however, before its widespread introduction.

Genetic variants

The very recent identification of 29 genetic variants that predispose towards prostate cancer offers another, more targeted, opportunity to reduce the death toll of this increasingly prevalent disease.[6]

Linkage studies in multiple case families have shown linkage to some regions, but searches for definitive genetic mutations arising from candidate gene screening in such regions have yielded conflicting results. Several research groups are now using candidate gene screening for rare variants and genome-wide association approaches to identify common variants. From the former of these types of studies, rare but high/moderate risk variants have been found in genes in the DNA repair pathway.

A recent genome-wide association study in DNA samples from prostate cancer cases and controls from the UK and Australia found that genetic variants on chromosomes 3, 6, 7, 10, 11, 19 and X were associated with prostate cancer risk and confirmed previous reports of SNPs associated with prostate cancer risk on chromosomes 8 and 17.

These discoveries raise the possibility of the identification of a sub-group of men who are especially susceptible to prostate cancer, in the same way that women who harbour certain genetic mutations are particularly prone to breast cancer. These men could be carefully scrutinised for evidence of prostate cancer by regular PSA measurements, as well as PCA3 testing and template prostate biopsies taken via the transperineal route, which would significantly reduce the risk of serious infection.[7]

TREATMENT OPTIONS

Local disease

Once prostate cancer has been detected, usually on the basis of a transrectal ultrasound-guided biopsy of the gland, and secondary spread of the disease excluded, the patient and his family are faced with the difficult decision about which treatment option to select.

In lower-risk cases, see table 1, above left, a programme of active surveillance may be sufficient. Regular PSA measurement at three-monthly intervals and an MRI and repeat biopsy are usually recommended to exclude local progression.[8]

Surgery: In fitter men, with more clinically significant disease, eradication of the cancer by surgical removal of the gland is often involved, indeed this is the only treatment which has been proven in a randomised controlled trial to reduce both the rate of metastases and mortality compared with watchful waiting.[9]

The traditional open technique of radical prostatectomy is now increasingly being replaced by the laparoscopic keyhole approach, with or without the assistance of the da Vinci robot. This sophisticated piece of apparatus allows 3D visualisation and 10 times magnification making the dissection of the neurovascular bundles and anastomosis of the bladder to the urethra more precise.[10-12]

Radiotherapy: Other treatment options for localised prostate cancer include brachytherapy, in which radioactive seeds are implanted into the prostate, and external beam radiotherapy, which is usually delivered over a six to seven week period.

Although both radiotherapeutic options can undoubtedly achieve complete cure, they do leave the patient and clinician in some uncertainty as to whether the tumour has been completely eradicated, as PSA values decline but do not reliably become undetectable as they do after surgery.

The same applies to the new treatment option of high-intensity focused ultrasound (HIFU) which, unlike radiotherapy, can be repeated but for the present should be regarded as experimental.

Metastatic disease

In contrast with localised or locally advanced disease, metastatic prostate cancer is associated with high mortality, approximately 70% within five years.

Androgen deprivation, which has become the mainstay of treatment, effectively reduces intraprostatic DHT concentration by more than 80%, resulting in reduced androgen receptor stimulation and increased prostate cancer apoptosis.

Androgen deprivation can be achieved by bilateral orchidectomy or treatment with LHRH analogues, and the value of adding an antiandrogen (maximal androgen blockade) is still debated. Pure LHRH antagonists are now available.

LHRH analogues: LHRH analogues, such as goserelin acetate, buserelin and leuprolide, are highly potent LHRH agonists (superagonists). After administration, there is a transient initial increase in LH secretion, and hence in testosterone secretion; this is followed by desensitisation (downregulation), resulting in a fall in LH and testosterone secretion. These agents can be delivered via one-, three- or six-monthly depot preparations administered subcutaneously or intramuscularly.

A potential side effect is tumour flare, which 8–32% of patients experience as a result of the initial transient increase (140–170%) in testosterone.[13] This may result in increased bone pain or worsening of symptoms of bladder outflow obstruction; spinal metastases may also be stimulated, increasing a risk of spinal cord compression.

Tumour flare can be avoided by prior and concomitant administration of an antiandrogen during the first six weeks of treatment. Comparative trials have shown that the response rates obtained with LHRH analogues are equivalent to those obtained after orchidectomy in terms of time to progression and overall survival.

LHRH antagonists: Recently the pure LHRH antagonist degarelix[14] has been introduced, and regulatory approval of a similar compound abarelix[15] is expected soon. These peptides inhibit LHRH release without the initial »

key points

SELECTED BY
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Prostate cancer is currently diagnosed in more than 34,000 men every year and claims more than 10,000 lives per annum in the UK. Recently, prostate specific antigen (PSA) population screening has been evaluated in two major randomised, controlled studies. Even though the more mature European study confirmed that PSA screening is capable of reducing prostate cancer mortality, anxieties still persist, particularly surrounding the issue of overdiagnosis of clinically insignificant cancer, which may never be destined to result in morbidity or mortality.

The very recent identification of 29 genetic variants that predispose towards prostate cancer offers another, more targeted, opportunity to reduce the death toll of this increasingly prevalent disease. It also raises the possibility of the identification of a sub-group of men who are especially susceptible to prostate cancer.

Once prostate cancer has been detected, usually on the basis of a transrectal ultrasound-guided biopsy of the gland, and secondary spread of the disease excluded, the patient and his family are faced with the difficult decision about which treatment option to select. In lower-risk cases a programme of active surveillance may be sufficient. In fitter men, with more clinically significant disease, eradication of the cancer by surgical removal of the gland is often involved, indeed this is the only treatment which has been proven in a randomised controlled trial to reduce both the rate of metastases and mortality compared with watchful waiting.

Metastatic prostate cancer is associated with high mortality – approximately 70% within 5 years. Androgen deprivation, which has become the mainstay of treatment, effectively reduces intraprostatic DHT concentration by more than 80%, resulting in reduced androgen receptor stimulation and increased prostate cancer apoptosis. LHRH analogues, such as goserelin acetate, buserelin and leuprolide, are highly potent LHRH agonists. After administration, there is a transient initial increase in LH secretion, and hence in testosterone secretion; this is followed by desensitisation, resulting in a fall in LH and testosterone secretion. A potential side effect is tumour flare, which 8–32% of patients experience as a result of the initial transient increase in testosterone.

In most cases, advanced prostate cancers treated with any form of androgen deprivation eventually begin to progress, a phenomenon known as hormone-refractory or androgen-independent disease. An increase in PSA level after initially successful androgen deprivation almost inevitably indicates impending clinical progression. Docetaxel, given in a 3-week schedule, is superior to mitoxantrone/prednisone in terms of decreasing disease progression, PSA response and improving pain. It also significantly improves survival.

stimulation seen with LHRH analogues by blocking pituitary receptors and thus they are not associated with a surge in testosterone i.e. a flare. This results in a more rapid achievement of the castrate state. More rapid return of testosterone with intermittent application is potentially an additional benefit. Currently they need to be administered by monthly injection.

Hormone-refractory disease

In most cases, advanced prostate cancers treated with any form of androgen deprivation eventually begin to progress, a phenomenon known as hormone-refractory or androgen-independent disease. An increase in PSA level after initially successful androgen deprivation almost inevitably indicates impending clinical progression.

This group is, however, quite heterogeneous, including men with PSA rises only and no demonstrable metastases, and men who have many bone and visceral metastases, pain and poor functional status; survival can range from only a few months to four years. Historically, therapy had little impact beyond modest palliation; however, treatments that may delay the progression of symptoms, as well as prolong survival, are becoming available.

Docetaxel, a chemotherapy agent which is a member of the taxoid family, induces apoptosis in cells through microtubule depolymerisation. It has been tested in a randomised trial against mitoxantrone and prednisone in men with androgen-independent prostate cancer.

The results of this study (TAX-327)[16] showed docetaxel, given in a three-week schedule, to be superior to mitoxantrone/prednisone in terms of decreasing disease progression, PSA response and improving pain. In addition, docetaxol significantly improved survival from a median of 16.4 months for mitoxantrone/prednisone to 18.9 months for three-weekly docetaxel, which correlates to a 24% relative reduction in death.

The side effects associated with docetaxel include neutropaenia, skin reactions and gastrointestinal problems. In the trial described, the incidence of these side effects was higher in the group receiving docetaxel than in the group receiving the mitoxantrone/prednisone combination.

Novel therapies such as endothelin A inhibitors, and a compound known as abiraterone, are in development, but none has been approved for clinical use yet by regulatory authorities.

CONCLUSION

Prostate cancer continues to touch the lives of large numbers of men of middle age and beyond, as well as their families. As a result of concerted efforts, both nationally and internationally, the evidence base for diagnosis and treatment of prostate cancer is steadily improving and with it the outlook for the very many individuals affected.[15]

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Useful information

Prostate UK
www.prostateuk.org
The charity provides information for healthcare professionals, patients with prostate disease and their families