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Prostate cancer – reasonable approaches to a confusing problem

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ABSTRACT Prostate cancer is the most common cancer in men. While progress has been made in understanding the disease's natural history and in developing more effective treatments, this has not clarified the disease's diagnosis and management – about which uncertainties have actually increased. In this article Dr Grahame Howard and Dr Duncan McLaren provide an overview of the current treatment options and their benefits.

KEYWORDS Cancer, prostate, PSA, prostatectomy, radiotherapy

LIST OF ABBREVIATIONS Gonadotrophin releasing hormone agonist (GnRH), high-intensity focused ultrasound (HIFU), magnetic resonance imaging (MRI), prostate-specific antigen (PSA), transrectal ultrasound-guided (TRUS)

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INTRODUCTION

One might think that with increasing knowledge about its natural history, more effective treatments, better diagnostic techniques and a much higher profile, there would now be clarity around the diagnosis and management of prostate cancer. Sadly, this is not the case and, if anything, the uncertainties surrounding diagnosis and treatment have increased. As a result, this disease remains one of the most difficult and challenging to manage. With an increasing incidence, making it now the most common cancer in men, a long natural history, even when metastatic, and significant disease and treatment-related morbidity, this is a burgeoning healthcare problem that can only increase in the future. For localised disease, there is continued controversy about immediate versus deferred treatment and which type or combination of treatments is optimal. For patients with metastatic disease, debate continues about the optimal timing of systemic treatment, whether or not more intensive combinations are better than sequential monotherapies and whether or not additional local treatment is indicated.

WHEN SHOULD A PROSTATE-SPECIFIC ANTIGEN TEST BE PERFORMED?

This possibly would read better as 'when should a PSA not be performed?' There are a number of reasons for doing a PSA. The first is to make a diagnosis of prostate cancer when there are symptoms of advanced or metastatic disease. Here it can be very helpful, and a raised PSA of more than 100ng/ml with a malignant-feeling prostate, possibly with evidence of bone metastases, will often be diagnostic, and treatment can be initiated without the need for a biopsy.

The second and most common reason is to diagnose localised asymptomatic disease at a stage when it may be curable. Urologists will routinely perform a PSA when patients are referred with lower urinary tract symptoms. This is because PSA is a surrogate for prostate volume as well as a screen for cancer and this may affect the management of the patient's symptoms. There is no value in doing this test if, having made the diagnosis of cancer, no treatment will be indicated due to age, co-morbidity or patient preference.

The role of population screening for all men over the age of 50 years is unclear and studies are under way that will hopefully clarify whether or not this is beneficial. However, whatever the outcome of these studies, screening is happening by default. Patients are requesting a PSA and healthcare workers are increasingly performing one as part of a general health check. The worst-case scenario for oncologists is for patients with a raised PSA to be referred for biopsy and treatment when, by virtue of age or other co-morbidity, treatment would not be advised. This leaves clinicians with a patient who has an expectation of treatment that can be difficult to manage. For the clinician, therefore, it is important to assess whether the patient is likely to be considered for localised treatment before doing the test.

The 'ten year' test is probably still a useful rule of thumb. That is, it may well be ten years before a localised cancer becomes clinically significant, and is the patient likely to survive that long? Patients requesting a test should be

counselled as to the process and significance of making the diagnosis and the uncertainties around treatment. It is the policy at the Edinburgh Cancer Centre to assess patients over 75 years of age with a raised PSA to avoid unnecessary biopsies. This policy is based on our audit data, which shows that in this age group a biopsy rarely affects management. Some clinicians have a lower threshold for performing a PSA in men with a first-degree relative with prostate cancer and those of Afro-Caribbean descent.

DIAGNOSIS AND STAGING

Unless there is clear evidence of metastatic disease with a high PSA of more than 100ng/ml, biopsies are necessary to confirm the diagnosis. Transrectal ultrasound-guided (TRUS) biopsies, although now routine, are not without morbidity and most patients find them an unpleasant experience. As well as being diagnostic, this will provide information on the volume and histological differentiation (Gleason score) of the cancer. This information will help inform decision-making as it provides predictive factors for progression and spread. Staging is necessary in all but those with a low PSA (below 10ng/ml) and well-differentiated (Gleason score 6 or less) cancers. This will normally involve a bone scan and magnetic resonance imaging (MRI) of the abdomen and pelvis.

TO TREAT OR NOT TO TREAT?

Having made a diagnosis of prostate cancer, a decision needs to be made as to which patients require treatment. For those with apparently localised disease, the histological Gleason score, local tumour extent (T stage), presenting PSA level, age and general health will all be taken into account. Increasingly, patient preference quite rightly plays an important role. This may on occasions result in patients receiving intensive combinations of treatments with curative intent when, in the clinician's view, they are more likely to die of diseases other than their prostate cancer.

Having decided that local treatment is indicated, there is then the question of which treatment is best. In essence, we have a choice between radical prostatectomy and radiotherapy, either external beam in combination with hormonal therapy or prostate brachytherapy. In the absence of randomised studies, we are left with the traditional tools of personal bias and clinical judgement. For this patient group, this is probably appropriate. There are specific indications and contraindications to the various treatments and it may be a relatively simple process to select the most appropriate treatment. Nonetheless, tailoring a number of different options to the individual still relies on good clinical judgement and an informed discussion with the patient.

If the disease has metastasised it is usual to advise treatment with hormonal therapy. Although the 'gold standard' is a gonadotrophin releasing hormone agonist (GnRH), there are other options, including oral antiandrogens and pulsed treatments, and the most appropriate treatment for each patient can only be made after a detailed discussion of options with particular regard to side-effect profiles. Although usually well-tolerated, hormonal treatment can prove devastating to a man's quality of life through reduction of testosterone to castrate levels.

A more difficult decision is when to treat a rising PSA, following radical local therapy, where there is no evidence of metastases. The rate of rise may be helpful in this situation. A slow rise over many years may not require any intervention, whereas a doubling time of less than six months probably should be treated with hormonal therapy. Salvage therapy after failed local radical treatment remains an area of ongoing research. There is particular interest in the role of cryotherapy or high-intensity focused ultrasound (HIFU). The role of salvage radiotherapy after prostatectomy is being addressed in ongoing clinical trials.

Standard treatment for metastatic disease in the UK is hormonal therapy, either monotherapy or maximal androgen blockade. The average duration of PSA response is 18–24 months before the disease becomes refractory. When hormone resistant, chemotherapy with docetaxel has been proven to offer benefit in terms of symptom control and quality of life, although the survival benefit is modest. There is now understandable interest in more intensive combinations of treatment including agents such as bisphosphonates, radioactive strontium 89, and new targeted drug therapies such as tyrosine kinase inhibitors. Until the results of trials assessing these combinations with their potential for increased toxicity are available, they cannot be considered to be standard therapy.

CONCLUSION

It is very unlikely that there will ever be one optimal treatment for men with prostate cancer because of the wide spectrum of the disease and of the patients it affects. It is therefore likely to continue to require the clinical judgement of experienced clinicians to advise patients who have this disease. The challenge with this disease is not only to cure those where it is possible and appropriate, but not to overtreat clinically insignificant disease and adversely affect the quality of life for those where there will be no benefit.

Further information can be obtained from:
http://www.prostate-research.org.uk,
http://www.prostate-cancer.org.uk,
http://www.prostatescotland.com.

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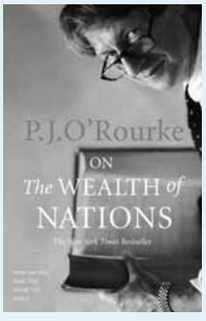
KEYPOINTS

- Prostate cancer is recognised increasingly and is now the most common cancer in men.
- Prostate-specific antigen is used increasingly to screen for asymptomatic localised cancer, though the benefits are uncertain; those at increased risk of prostate cancer include individuals with prostate cancer in a first-degree relative and Afro-Caribbean men.
- Prostate specific antigen >100ng/ml in patients with clinical evidence of metastatic disease allows prostate cancer to be identified as the cause and treatment to be given without the need for biopsy.
- Diagnosis otherwise requires a prostate biopsy, and the extent of the cancer is identified by imaging.
- Careful consideration is needed before prostate biopsy and local prostate treatment is carried out for patients unlikely to survive for ten years.
- Local treatments for prostate cancer include surgery (radical prostatectomy) or radiotherapy (external beam or brachytherapy).
- Metastatic disease usually requires hormonal treatment, and gonadotrophin releasing hormone agonists are the 'gold standard' drugs.
- Cryotherapy and high-intensity focused ultrasound are among the treatments being developed for use when local treatment fails.
- Advising curative treatment when appropriate and not doing so when it is unnecessary requires experience in clinicians managing this disease.

A BOOK YOU SHOULD READ



Author:
PJ O'Rourke
Title:
On The Wealth of Nations
Publisher:
Atlantic Monthly Press, 2007

Adam Smith, widely regarded as the patron saint of capitalism, is frequently quoted in support of a global economy that has raised production to unprecedented levels and has, in the process, made the rich super-rich and the poor, in too many instances, super-poor. Smith's most famous work is *The Wealth of Nations*, published in 1776, and, as it is a substantial work, it will come as no surprise that it is much more quoted than read.

PJ O'Rourke's commentary on *The Wealth of Nations* and on Smith's 1759 book *The Theory of Moral Sentiments* is not casual reading, but it is enjoyable and instructive and provides a healthy antidote to the frequently inaccurate and often self-serving uses to which Smith's work is put.

Smith's aim in writing his two great books was to improve people's lives, and to understand his views both books must be considered. He tried to find out how an understanding of morality, economics and government could lead to better behaviour, greater wealth and improved political conditions.

Moral Sentiments attributes moral behaviour to natural human sympathy (or feeling) for others, combined with the gradual development of a personal independent spectator (or conscience) through which actions can be judged. This promotes moral decisions that balance one's own interests with the interests of others.

The Wealth of Nations points out that production (the only purpose of which is consumption) is increased by workers promoting their own interests, by division of labour (specialisation) and by freedom to trade. It also underlines that equal rights, including the right to own property (the rule of law), are necessary for this to function most effectively.

Smith took a generally dim view of governments as they never followed his criteria for wealth creation, but he recognised their importance in regulating what we recognise as capitalism and in being free from the self-interest of the rich and powerful in doing so.

Smith is a good source of quotations. He believed that workers improve their position best by their own efforts ('Nothing can be more absurd than to imagine that men in general should work less when they work for themselves, than when they work for other people'), but that the interests of traders and manufacturers were 'always in some respects different from, and even opposed to, that of the public'; that profit was desirable but that 'pernicious gains' were not; and that free competition forced the profit-maker to sell goods at 'the lowest [price] at which he is likely to sell them … at least where there is perfect liberty' (a situation that is not usually present).

Finally, though Smith approved of the division of labour, doctors might like to contemplate his view of overspecialisation: 'The man whose whole life is spent in performing a few simple operations … generally becomes as stupid and ignorant as it is possible for a human creature to become.'

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