



ACROSS THE SPECTRUM OF PROSTATE CANCER

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Abstract

Early detection of prostate cancer has focused on the prostate specific antigen testing debate, however decision aids to help men weigh the pros and cons of testing, and then guidelines based on evidence about when to test and how to respond to the result, will provide better guidance. Adding other prostate specific antigen related tests has not yet alleviated uncertainty, but imaging with multi-parametric MRIs may be more helpful identifying cancers of high risk. The development of prostate specific membrane antigen PET/CT holds even greater promise in providing higher sensitivity and specificity. For those requiring surgery, the comparative value of robotic surgery and radical prostatectomy may only emerge from randomised trials. In non-organ confined prostate cancer, prospective studies are needed before cytoreductive surgery is firmly established as part of a multimodal management. The mainstay of treating metastatic disease has been androgen deprivation therapy with luteinizing hormone-releasing hormone analogues and anti-androgens, but now androgen signalling inhibitors are finding a place in castrate resistant disease. The sequencing of these drugs in relation to the taxanes in this situation needs further investigation, but taxanes may also have a place in castration-naïve disease as part of initial therapy with androgen deprivation. The role of supportive care by prostate nurses is being investigated, and how best to support prostate cancer survivors requires ongoing research.

This Forum examines current issues in prostate cancer, spanning the spectrum from early detection to survivorship, and the emerging treatments in between. In Australia, prostate cancer is the highest incidence cancer in men, estimated at over 20,000 cases in 2014 and is responsible for nearly 3300 deaths each year.

Early detection would be ideal, but the two large randomised studies to try to demonstrate whether prostate specific antigen (PSA) testing and early detection resulted in a survival advantage, gave conflicting results, and yet men who were treated could have their quality of life compromised by side-effects such as impotence and incontinence. Evidence-based guidance is needed for men who, having had the risks and benefits explained to them, choose to have a PSA test. The Prostate Cancer Foundation of Australia and Cancer Council Australia are producing guidelines to inform this situation and a summary of their current progress is reported. These provide some certainty around how often to repeat the PSA test, when a biopsy is desirable, and the options for managing the findings of biopsy.¹

The identification of PSA, the introduction of ultrasound-guided prostatic biopsies and the introduction of nerve sparing radical prostatectomy have dramatically changed the clinical landscape for prostate cancer. However, while leading to increased diagnosis of localised cancer that is now capable of cure, it has also led to unnecessary biopsies and the diagnosis of low grade cancers and resultant over-treatment. Gordon and colleagues have chronicled the attempts to improve the sensitivity and

specificity of PSA.² PSA velocity (the rate of change in PSA concentration) and PSA density have been used, and while of some benefit, they are still far from perfect. They note the use of the prostate health index, which has been reported to be better at predicting prostate cancer, particularly in obese men, but its role in decision making still needs to be established. Early studies with an aberrant glycosylation PSA assay demonstrated a sensitivity of 95% and a specificity of 72%. The use of 4 kallikrein proteins to establish a 4K score showed a high level of discrimination in detecting Gleason scores of greater than seven cancers, nevertheless both studies will require further confirmation. The PCA3 test was hoped to be superior to PSA. However, the authors indicate it has yet to be established as a stand-alone investigation and further studies are being undertaken using PCA3mRNA. Perhaps the most promising initiative is the use of multiparametric MRI. This modality appears to differentially identify high risk cancers, which would reduce the need to biopsy all men with raised PSAs. However, the authors identify the risk of missing some high grade tumours, the requirement for expert interpretation and the issues surrounding cost as ongoing concerns.

It would be helpful to adopt more imaging techniques as this could not only better delineate disease location, but better characterise disease biology at initial diagnosis and again at relapse. Imaging is able to further assess the weight of which should be accorded to elevated PSA tests. MRI-guided biopsies are more accurate than traditional ultrasound guided biopsies and multiparametric MRI can provide more accurate staging, both initially and

at relapse, which better guides treatment decisions. FDG PET and PET CT have a limited role for staging high grade disease, but Hicks et al outline the emergence of prostate specific membrane antigen PET/CT, a promising new technique with higher sensitivity and specificity.³

Frydenberg and colleagues have examined the relative benefits of robotic assisted radical prostatectomy (RARP) versus open radical prostatectomy (ORP).⁴ Rather surprisingly, although robotic surgery was introduced over a decade ago, the level of evidence to support the superiority of the technique is poor. Using positive margins as a surrogate marker for surgical quality and hence cancer control, there appears to be little difference between the two approaches. Looking at the common complications of radical prostatectomy, incontinence appears to be reduced in the case of RARP. However, the studies were not controlled for body mass index, comorbidity index or surgeon experience. In the case of erectile dysfunction, there seems to be more consistency regarding the benefit of RARP. Although RARP appears to be superior to ORP with regard to blood loss, there is wide variation in the level of blood loss reported in the various studies. Length of stay appears to be superior by one day over ORP, however, the cost of RARP is around double that for ORP. Consistently in the papers cited, the authors raise the importance of surgical experience and their concern at the failure to take this into account when comparing studies. The authors also highlight the difficulties of ensuring surgeons are appropriately trained and that the transition from a competent ORP surgeon to a competent RARP surgeon is not a simple process and requires considerable case experience. They are optimistic that the only randomised trial of RARP versus ORP, which has commenced, may finally establish the relative value of the two approaches.

Sathianathan and colleagues have examined the role of cytoreductive prostatectomy in non-organ confined cancer.⁵ Given the data supporting the value of cytoreductive surgery in breast, renal and ovarian cancer, interest has begun to be focused on the small percentage of men who present with non-organ confined prostate cancer. This is further encouraged by the poor survival rate of men with non-organ confined cancers - a five year survival rate of 28% compared with 100% in organ confined disease. However, it is evident that men over the age of 70 and with a PSA above 20ng/ml are less likely to benefit. It appears that men with a low burden of metastatic disease are most likely to benefit from cytoreductive surgery. However, a major challenge is the ability to truly establish that a man has low volume disease. While results are promising, there has been only one study evaluating the safety of cyroreductive radical prostatectomy, and as the authors indicate, further prospective studies are needed before cytoreductive surgery is firmly established as part of a multimodal approach to non-organ confined prostate cancer.

The mainstay of treating metastatic disease has been androgen deprivation therapy with luteinizing hormone-

releasing hormone analogues, anti-androgens, five alpha-reductase inhibitors such as dutasteride, and gonaatrophin hormone releasing antagonists such as degarelix. These work until castration resistance. Tilley's group highlights the role of the androgen receptor in this process and emergence of the androgen signalling inhibitors, abiraterone and enzalutamide, which can be added to the cytotoxic agents currently used for castration resistant disease.⁶

The taxanes are the mainstay of chemotherapy for prostate cancer, and although they had resulted in only modest improvements in survival, they have improved symptom control and quality of life in metastatic disease. Davis and Pezaro outline the introduction of carbazitaxel for taxane resistant disease.⁷ The emerging question however, is whether these agents work as well after the androgen signalling blockers, so it will be important to investigate the sequencing of these drugs. The recent CHARTED and STAMPEDE studies go further and suggest that the optimal use of docetaxel may be up front when androgen deprivation therapy is commenced in castration naïve prostate cancer.^{8,9}

When considering the advances in the management of prostate cancer, it is important that the patients receive good supportive care. Sykes, on behalf of the Prostate Cancer Foundation of Australia, reports on their Prostate Cancer Specialist Nurse Program.¹⁰ The nurses have broad roles in ensuring that patients are aware of their pathways of care and receive good supportive care. The nurses had multiple roles within the multidisciplinary team. They want men and their carers to be satisfied with their treatment and to ensure that men have sufficient information to make informed choices about their treatment.

With an increasing incidence of prostate cancer and better survival, research into the issues of surviving prostate cancer, the economic impact of managing this group and the disparities in management due to socioeconomic status or location is essential. This is what Chambers' group is doing,¹¹ Mens' ongoing psychosocial and psychosexual needs are important components of their continuing quality of life. There are new insights into the benefits of exercise for the mental and physical health of those with prostate cancer and the amelioration of the side effects of therapy. Ongoing research will need to involve the whole community, with the patient and carer as the focus.

References

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