CANCER FORUM

Cancer Council Australia

Clinical Oncology Society of Australia

November 2015
Volume 39 Number 3

cancerforum.org.au

CANCER FORUM

Cancer Forum is produced by Cancer Council Australia for health professionals working in cancer control.
It is the official journal of the Clinical Oncology Society of Australia.

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The policy of *Cancer Forum* is to provide a forum for debate and the exchange of medical, scientific, political, social and educational comment related to cancer research, treatment, prevention and control. *Cancer Forum* invites submissions of original research articles, reports and letters relating to these themes.

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Cancer Forum is published in March, July and November and is available online at cancerforum.org.au

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Design by Wolff Design
Printed by SOS Print & Media

CANCER FORUM

November 2015 Volume 39 Number 3 ISSN 0311-306X

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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 kallekrien 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.

Sathianathen 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 gondatrophin 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 CHAARTED 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.

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HIGHLIGHTS OF PSA TESTING GUIDELINES

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Abstract

These guidelines aim to provide the evidence that is available to guide clinicians managing men who, after the risks of benefits of Prostate-Specific Antigen testing are explained them, choose to have the prostate test. Two large population studies have defined risks and benefits but have conflicting results. The guidelines commissioned by the Prostate Cancer Foundation of Australia in collaboration with Cancer Council Australia, suggest that men who ask for testing should be tested every two years from the ages of 50 to 69. No survival benefit occurs until seven years. A Prostate-Specific Antigen of 3 ng/ml triggers further testing, with a biopsy for a Prostate-Specific Antigen greater than 5.5 ng/ml with lesser Prostate-Specific Antigen concentrations triggering biopsies in younger men. Low risk patients may have the option of active surveillance which delays their definitive treatment, while for those where cure is not a goal, watchful waiting may be suggested, with symptoms being the reason for further treatment.

The controversy over whether asymptomatic men should be screened by a prostate-specific antigen (PSA) test for prostate cancer arose because some men who had the test were subsequently found to have aggressive prostate cancer at a time when they could be cured. However, many more asymptomatic men who had an elevated PSA test were diagnosed and treated for an indolent prostate cancer, which would never have led to their deaths if left undetected, yet they were exposed to the same side effects of possible impotence and incontinence. The PSA test itself is not specific for prostate cancer and so false positives can occur (87 of 1000 will have a false positive PSA that will lead to a biopsy.[1] False negatives also occur.

Advocates for screening have argued that maximising the lives saved should be the major consideration. However, two large randomised studies to determine the benefit of PSA screening, the Prostate Lung Colorectal and Ovarian Cancer Screening Trial (PLCO) from the US and the European Randomised Study of Screening for Prostate Cancer (ERSPC) yielded conflicting results.[2,3] PLCO showed no survival advantage for the men who were screened by PSA testing (in fact a non-significant 13% decrease at 13 years). The ERSPC showed a mortality advantage of 21%.

The 13 year follow-up of ERSPC gives a good idea of the balance between benefits and harms.[4] For every 1000 men tested, 1.28 deaths were prevented, and 27 cancers were diagnosed to prevent one death. These results show why population screening, which would recommend that every man be tested, is not being pursued. However, guidance is needed for how to manage men who, having had the potential risks and benefits of PSA testing explained, request a PSA test. The National Health and Medical Research Council (NHMRC) released a document explaining the risks and benefits of testing to help general practitioners.[5]

The Prostate Cancer Foundation of Australia teamed with Cancer Council Australia, who produce treatment guidelines, to use strict evidence-based guidelines methodology to explore the question of PSA testing for those men who request it. This involved producing the guidelines to a standard that could be endorsed by the NHMRC. An expert multidisciplinary team to write the guidelines was selected. Structured clinical questions were identified and systematic literature reviews including searches for existing guidelines performed. The papers were screened against predefined eligibility criteria and then appraised for quality. The level of evidence was determined

and then recommendations made, the strongest of which are evidence-based which can be distinguished from those based on consensus. Following is a summary of the key and evidence-based recommendations which were circulated for public discussion in December 2014.[6]

Recommendations are given levels of evidence depending on whether there were systematic reviews of randomised trials (level I), randomised trials (level II), non-randomised comparisons or single arm studies (level III) or case reports (level IV). The evidence is graded from A to D, where A is evidence that can be trusted to guide practice, and D is weak evidence applied to practice with caution.

Recommendations

The guidelines did not attempt to provide guidance about the decision of whether to have a PSA test. That will be covered by a decision aid to be produced subsequently. There is evidence that such aids improve knowledge and satisfaction and reduce distress at having to make the decision about whether to have a PSA test.[7]

PSA testing

For men, who after considering the potential benefits and harms of PSA testing, decide to have a PSA test, what should the frequency of testing be? It is recommended that regular testing is offered every two years from age 50 to 69 and further testing if the PSA is greater than 3 ng/ml (grade C).[8] In a consensus-based recommendation, it was considered that in men with a risk 2.5-3 times higher than average (e.g. a brother with prostate cancer diagnosed before 60 years) who decide to undergo testing, the testing can start earlier at 45 years. For those at even greater risk, 9-10 times average (e.g. by having a father and brother with prostate cancer) and who choose to be tested, they can start at 40 years.[9] In those studies which showed a mortality benefit from the early diagnosis of prostate cancer due to PSA testing, the benefit is not seen until about seven years after the PSA test.[10] Therefore if a man has concomitant illnesses and is unlikely to survive seven years, then there is no possible benefit that can be gained from PSA testing, and so it is not recommended (grade C). In fact, you may see the short-term harms from resulting therapy without the possibility of survival benefit.

Digital rectal examination

An interesting result of reviewing the evidence is that in the primary care setting in an asymptomatic man where a PSA has been performed, digital rectal examination (DRE) on balance will not add anything meaningful and is not recommended (grade C). This may be a relief to both men and their general practitioners! However, a urologist may gain useful information from a DRE prior to biopsy.

Biopsy

When should a decision be made to biopsy? In the 50 to 69 age group, the evidence suggests that if the PSA is greater than 3 ng/mL, a repeat PSA should be done in one to three months, along with a free to total PSA percentage if the reading had been 3.0 to 5.5 ng/mL (grade D). The consensus view is that if the PSA is greater than 5.5 ng/mL, a biopsy is warranted. A further indication for biopsy is if the PSA remains from 3.0 to 5.5 ng/mL but the free to total PSA percentage is below 25%.[12] The use of PSA velocity (grade D) or prostate health index is not known to increase the specificity.[13] If a man in this age range with a PSA of greater than 3 is not offered or refuses biopsy, the consensus is that he should be advised to repeat the PSA in two years as there is a small chance of missing a significant cancer.

For men 45 to 69 years with a PSA in the range of 2.0 to 3.0 ng/ml, a biopsy should be considered if the free to total PSA is less than 25% (grade D).[14]

In terms of the yield of the biopsy, there is level I evidence that 24 cores nearly double the odds of detecting cancer as compared to six, therefore in addition to the sextant biopsies, directing an additional 15-18 biopsies to the peripheral zones of the prostate is recommended (grade B).[15] There is insufficient evidence to make an informed choice between the transrectal and transperineal approaches.

If the biopsy is negative, what is the follow up? There is evidence that for each additional year after a negative biopsy, there is a 1-10% greater risk of prostate cancer at re-biopsy (level 1), so men should continue to be followed.[16] Men should be monitored more closely if they had an abnormal pre-biopsy DRE, or biopsy finding of either atypical small acinar proliferation or high-grade prostatic intra-epithelial neoplasia. As well as repeat PSA, follow-up imaging to help target a tumour for follow-up biopsy should be considered (grade D). A multiparametric MRI (magnetic resonance image), in centres with expertise in performing these tests, should be considered for men with a negative ultrasound-guided transrectal biopsy, to determine if another biopsy is needed. If negative, no further biopsy will be required unless there are the higher risk features that warrant the closer monitoring above (grade D).[17,18]

Active surveillance

Patients who on biopsy have a low risk prostate cancer can have immediate treatment or opt for active surveillance, where they are followed up regularly so that potentially curative treatment can be offered when there are signs of progression. The evidence for what constitutes low risk suggests that patients with a PSA less than or equal to 20 ng/mL, clinical stage T1-2 or Gleason score 6, can be offered active surveillance (grade C). Others should be offered treatment unless they refuse, when it may be appropriate to re-biopsy them.[16,19]

The consensus is that the follow-up on active surveillance should be a PSA every three months with a DRE every six months. Repeat biopsies could be offered every two or three years or earlier if there were signs of progression.

Watchful waiting

Watchful waiting is a strategy in asymptomatic men for delaying definitive treatment until symptoms occur or the disease progresses, when the aim is to palliate the symptoms, not cure the disease. For men with potentially curable prostate cancer, the risk of developing advanced prostate cancer and dying is greater than if they have immediate treatment, however they are unlikely to have a diminished quality of life in the medium to long-term (grade C). Given that the literature shows that a survival advantage resulting from PSA testing is only seen after seven years, if due to concomitant illness a man's life expectancy was less than seven years, watchful waiting would be a reasonable strategy.

The consensus is that initially these men should be followed by their general practitioners with PSA testing every three to four months for the first year, and if little change every six months thereafter, and referred back for specialist opinion for sudden progression of PSA or symptoms.[20,21]

Conclusions

These guidelines serve to show where current recommendations around the risks and benefits of PSA testing are based on evidence and where there is consensus. They are working towards maximising the benefits of PSA testing for men, while reducing the harms to individuals which would occur from unselected population testing. They show where more data would be desirable, particularly in being able to select those whose lives would be saved by immediate treatment. They will help plan for how best to test and follow-up men who after the risk and benefits of PSA testing are explained, wish to be tested.

The guidelines have been produced on a wiki platform, so that they are easy to update as new evidence becomes available and easy to disseminate. Decision aids based on the evidence available will follow.

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CHANGING STATUS OF INVESTIGATIONS FOR PROSTATE CANCER DETECTION

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Abstract

Before the introduction of serum prostate specific antigen for the early detection of prostate cancer, this condition was diagnosed at an advanced stage, with palliative androgen deprivation therapy the mainstay of management. Increasing use of prostate specific antigen testing has resulted in a significant stage shift from locally advanced/metastatic disease to early stage, lower volume prostate cancer. Prostate specific antigen testing provides the potential for life-threatening disease to be detected early enough for effective treatment. However, many asymptomatic men with low-risk prostate cancer have also had what were, in retrospect, unnecessary diagnostic procedures and treatments leading to management-related morbidity. This manuscript traces the changes that have occurred and are occurring to refine detection, with the integration of new technologies to uncouple diagnosis from management so that potentially curative treatment can be tailored to those who are most likely to benefit.

Clinical detection of prostate cancer is evolving at a rapid pace, with the levels of imprecision experienced until very recently in the process of being superseded. However, before considering any investigation, the basic question of whether a diagnosis of prostate cancer will benefit the patient should be addressed. Many men have co-morbidities, the gravity of which will lead to their premature demise and of which they are completely unaware. This poor appreciation of individual life expectancy is not just limited to patients, as many clinicians are overoptimistic and 'give patients the benefit of the doubt' when recommending investigations and treatments.[1] In addition, individual wishes with respect to quality of life should be respected,[2] in particular the importance some men place on sexual function, given the impact that all prostate cancer treatments can have on erectile ability and other bodily functions.

Because of the long natural history of prostate cancer, expectation of a 7-10 year life expectancy following treatment (and therefore, diagnosis) is considered warranted in terms of a survival. Consequently, many patients will not live long enough to achieve a survival benefit.[3-6] Life expectancy is certainly not the only consideration, but it is for survival reasons coupled with the acknowledged potential adverse effects of investigations and treatment, that selective, rather than mass population or opportunistic, prostate-specific antigen (PSA) screening is advocated.

Men proceeding for prostate cancer screening are assessed initially by total serum (PSA) testing with or without digital rectal examination (DRE), findings influencing a decision whether to proceed to biopsy for a histological diagnosis. As most prostate cancers detected are impalpable, transrectal ultrasound (TRUS) is employed to permit spatial positioning of, previously six (sextant) but now >10-12, random biopsy needles, as the majority of early prostate cancers are unable to be differentiated from non-cancerous tissue with grey-scale ultrasound imaging. Increasingly, the transperineal approach to biopsy is replacing the transrectal route since anterior lesions constitute up to 30% of malignancies and these can be missed with the transrectal approach, especially in larger prostates, identified as being greater than 30mL.[7,8]

Prostate-specific antigen

PSA is a member of the kallikrein family of proteases, with PSA (KLK3) protein present in seminal fluid and with very low levels normally in blood. Clinical use of PSA began in the 1980s, initially having been approved by the Food and Drug Administration in 1986 for monitoring of the disease status of prostate cancer patients. In 1994, it was endorsed for prostate cancer screening,[9] with this application having caused controversy largely because of false positive results for insignificant or non-life-threatening tumours. The PSA blood test is a continuous variable with no cut point.[10] As a result, very low levels do not

completely exclude prostate cancer, although the higher the serum PSA, the greater the likelihood of malignancy, particularly in the absence of clinical infection.[11]

Abnormal levels of PSA do not distinguish between cancer and non-cancer, or identify those patients with prostate cancer who will benefit from attempted curative treatment. An elevated serum PSA merely indicates an abnormality in the prostate, with most PSA increases not attributable to prostate cancer. Furthermore, for those in whom prostate cancer is detected, many have indolent disease that will not show evidence of clinical progression in the short to medium term.[12]

When identifying those likely to benefit from a prostate cancer diagnosis and therefore PSA testing, a family history, particularly in first-degree relatives, is well-recognised to predispose to a future diagnosis of prostate cancer, but a PSA >90th percentile for men <50 years is regarded as even more predictive than either family history or race.[13] Hereditary prostate cancers occur more commonly than any other tumour diagnosed, on average six years earlier than for sporadic cancer.[14] Those patients with a family history of germ-line mutations in the family-susceptibility genes BRCA1 and BRCA2, have a significantly increased susceptibility for developing this malignancy, tending to present at a younger age, have more aggressive disease and poorer survival outcomes.[15-19]

PSA is a labile enzyme that can be affected by a variety of factors. Recent ejaculation elevates serum PSA for up to 48 hours, with vigorous exercise, bacterial prostatic infection, recent instrumentation and benign prostatic hyperplasia also incriminated as causes for raised levels in sera. The prostate gland enlarges as men age, so that age-based reference ranges are provided by many laboratories.[20] Instrumentation of the prostate and urinary tract can also raise PSA levels.[21] Drugs that inhibit 5-ï-reductase activity result in a decrease in serum PSA, with both finasteride and dutasteride reducing PSA values by approximately 50%.[22,23] Once a nadir is reached by these drugs, which target the benign prostatic heperplasia component of prostatic enlargement, reducing its contribution to serum PSA levels, PSA becomes a more sensitive marker for prostate cancer. Marks et al reported a 71% sensitivity and a 60% specificity for prostate cancer detection for men receiving dutasteride, recommending that an increase in PSA of >0.3 ng/ml from nadir should be regarded as an indication for biopsy in these patients.[24]

Despite the introduction of variations to PSA (below), it is serum PSA itself that is used almost exclusively for triaging patients for further investigations.[25] Another important role that PSA serves is aiding patient reassurance, an aspect so often overlooked in critical assessments of clinical practice. A serum PSA <1 ng/mL in a man aged 60 years has been reported to indicate an extremely low risk of significant prostate cancer in his lifetime.[26,27] Although the likelihood of diagnosing prostate cancer is relatively low in men aged less than 55 years, a subgroup with PSA levels >95th percentile is particularly at risk of developing life-threatening prostate cancer,[13,25] and it is the 'young man cohort' under 65 years which is the one most likely to benefit from diagnosis (and treatment) because these men are more likely to live long enough.[28] An analysis of the Victorian Prostate Cancer database between 2001 and 2008 showed that, in keeping with the rest of Australia, 1/3rd of prostate cancers were detected in men aged less than 65 years and, among those detected in men aged less than 65 years, 76% were Gleason score less than or equal to 7.[29]

Variations on PSA

Attempts to improve the predictability of serum PSA for prostate cancer detection have included measuring the rate of PSA change or PSA velocity and the relationship of PSA level in serum to the size of the prostate or PSA density. In some cases this is extended to include measuring transition zone volume, the site of benign prostatic hyperplasia and a low likelihood of significant prostate cancer. Although serial serum PSA readings often rise and fall over a relatively short period, an increase in >0.75 ng/mL in a year has been equated to and is generally regarded as indicating an increased risk of prostate cancer.[9] However, because malignancy is only one cause of an elevation in PSA, this relationship is far from perfect.

Similarly, measurement of prostatic size by transrectal ultrasonography is less than accurate, although serial measurements may be helpful in managing patients on active surveillance for low-risk disease. Nevertheless, a PSA density >0.15 ng/mL per gram of prostate tissue is generally considered worrisome for prostate cancer. The free or unbound PSA in relation to total PSA level in serum is commonly measured with a higher free component related to a lower likelihood of prostate cancer. A free component of <9% is particularly associated with malignancy. Measurements of free or unbound PSA levels are considered more useful in younger men and those with PSA values between 4 and 10 ng/mL.[30]

More recently, the prostate health index has become available and promoted. This test, that stratifies patients into three groups indicating probability, is calculated by having the value of a truncated form of the PSA molecule (proPSA) as the numerator and the free PSA value as the dominator, multiplied by the total PSA level to give a prostate health index reading. In one study, for a PSA 2-10 ng/ml, sensitivity, specificity and AUC (0.703) of PHI exceeded those of total PSA and percentage free PSA. Increasing PHI was associated with an increased risk of prostate cancer.[31] It is reported to be better at predicting prostate cancer risk than total PSA,[32] particularly for obese men,[33] but its role in decision making has yet to be established in Australia and other countries.

Two publications from last year are also of particular interest, although not yet widely available for clinical use. Yoneyama et al reported that a prostate cancer-associated

aberrant glycosylation PSA assay in sera from 314 patients who underwent biopsy Dep(138 prostate cancer: 176 non-prostate cancer) with PSA of <10.0 ng/ml, provided a sensitivity of 95% with a specificity of 72%.[34] Secondly, Parekh et al measured 4 kallikrein proteins (total PSA, free PSA, intact PSA and human kallikrein 2) in blood from 1012 patients from 26 US centres prior to prostate biopsy-470 men (46%) were diagnosed with prostate cancer, 231 (23%) of whom had Gleason >7 lesions. The predictive accuracy of the 4Kscore showed a high level of discrimination in detecting Gleason >7 lesions, with an AUC of 0.82 with a sensitivity of 84% and a specificity of 75%.[35]

PCA3 Test

Multiple markers have been examined as indicators of prostate cancer, mostly in blood, urine or voided urine following firm DRE or prostatic massage. Of these, the 'PCA urine test' is best known.[36-41] This test analyses the first part of a specimen of voided urine after milking the prostate by firm digital rectal examination or prostatic massage to dislodge prostatic fluid and cells from the posterior part of the gland.[42] At the commonly used PCA3 score cut off of 35, the PCA3 test has been reported to improve detection of prostate cancer compared with PSA in a pre-screened population, but its role in initial assessment of patients suspected of having prostate cancer has yet to be established as a first-line, stand-alone investigation.[37,43] Addition of other RNA markers to the 'PCA3 urine test' such as the fusion gene TMPRSS2:ERG, has been reported in some, but not all cases, to improve prostate cancer prediction.[38-41,44,45] It is because of the limitations of PCA3 and other tests that Noviogendex and DDL Diagnostic Laboratory (the Netherlands) are developing a 4-gene panel (Quattro) commercially around PCA3 mRNA.

Multi-parametric MRI

Following the initial work of Zerbib and colleagues in 2005,[46] MRI techniques have been developed to fulfil an increasingly valuable role in identifying evasive anterior and other significant tumours that may be missed by 'blind' TRUS biopsies.[47] Diagnostic images are provided by T2 diffusion-weighted MRI (capitalising on the mobility of water affected by interaction with intracellular elements, macromolecules, cell membranes and microstructures with differences observed in several cancers) in T2-weighted images and early gadolinium blushing due to increased vascularity in tumours.[48]

The potential for multiparametric MRI (mpMRI) to increase detection and identify the site of significant cancers so that biopsies can be targeted, is being exploited increasingly in routine diagnostic approaches. A combination of anatomical (T2-weighted) images with at least two of the three functional MRI parameters (diffusion-weighted imaging, dynamic contrast-enhanced imaging and spectroscopy) has been estimated to identify approximately 90% of moderate to high risk lesions, although less reliable for detecting small (<0.5 cc) and lower risk tumours.[49,50] Using a structured scheme, prostate imaging-reporting and data system (PI-RADs),[51] PI-RADS 3 lesions are at intermediate risk of being malignant, PI-RADS 4 probably malignant and PI-RADS 5 highly suspicious of malignancy.[52] Although a small number of significant prostate cancers will be missed if only patients with PI-RADS 3-5 lesions are biopsied, over 80% of indolent/low risk tumour patients and the majority of those with a raised PSA who do not have cancer will be spared biopsies and its risks of adverse effects.

mpMRI is an expensive investigation requiring expert interpretation, so its benefits need to be maximised if it is to be used to triage all men suspected of harbouring significant prostate cancer. Since most patients with a raised PSA +/- an abnormal DRE will not have any detectable prostate cancer, let alone clinically significant prostate cancer, cost effectiveness, in addition to oncological and quality of life benefits, demand scrutiny. A recent study performed in the Netherlands assessed the cost-effectiveness of mpMRI and MR guided biopsy compared with TRUS biopsy. The authors concluded that the total costs of the MRI strategy were almost equal with those of standard of care, and that a reduction of over diagnosis and over treatment with the MRI strategy led to an improvement in quality of life.[53] These findings may not translate internationally, and a major concern with MR guided biopsy is the extra time in the MRI-suite with the potential to expand costs further in what is already an expensive diagnostic process. In some centres, information from business cases (without MR guided biopsy) has contributed to mpMRI being used routinely to stratify patients into those likely to have significant prostate cancer compared with those whose glands are unlikely to harbour a clinically-significant malignancy,[54] so PI-RADs mpMRI 1 and 2 patients do not routinely proceed to diagnostic biopsy.

With the rapid introduction of mpMRI into the diagnostic equation, a number of issues remain to be resolved. Among these is the risk of missing a clinically significant Gleason 7 or greater tumour by restricting biopsies in the first instance to PI-RADs 3-5 lesions, although current data suggest that this is <15% for normal PI-RADS 1 or 2 MRI. Another quandary needing to be addressed is which lesions to biopsy with the patient on the MRI machine. MRI in-gantry biopsy may improve the diagnostic accuracy in some small lesions, but is not required for most tumours identified on MRI, which usually can be targeted adequately by transperineal or TRUS techniques, especially with evolving MRI-TRUS fusion technology.

MRI-based imaging is becoming established as an essential part of the diagnostic strategy for prostate cancer. It is notable that most advances in mpMRI per se have been prostate-centric, as mpMRI alone fails to indicate regional and more distant spread of tumour. On complete removal of the gland (radical prostatectomy) however, approximately 40% of patients have extra-

prostatic extension in the surgical specimen and 25% show ongoing evidence of cancer activity via a rising serum PSA, indicating unidentifiable occult metastases.[54,55] MRI research to improve rates of detection, both within the gland and at the sites of metastases, is being pursued actively, with initiatives including examining potential new markers, field strength changes and sequence optimisation.[56,57]

Prostate-specific membrane antigen PET

Over the last few years, positron emission tomography (PET) has begun to be used to identify metastases. PET imaging reflects function/dysfunction, thus adding a further dimension to imaging when superimposed on to CT and MR images. Many PET tracers have been tested for use in the evaluation of prostate cancer patients based on increased glycolysis ((18)F-FDG), cell membrane proliferation by radiolabeled phospholipids ((11)C and (18)F choline), fatty acid synthesis ((11)C acetate), amino acid transport and protein synthesis ((11)C methionine), androgen receptor expression ((18) F-FDHT), and osteoblastic activity ((18)F-fluoride), with ligands in the form antibodies or smaller molecules such as peptides and aptomers also having been used to deliver detectable labels to the prostate. Combining CT or MRI with PET adds anatomical precision vital in targeting interventions, with the potential of not only demonstrating local extension and metastatic disease, but also improving identification of significant intraprostatic prostate cancer concurrently, highly relevant if focal treatments to the primary lesion are to be contemplated.

Of those candidates examined to date in prostate cancer, prostate specific membrane antigen (PSMA) and choline seem the best, with PSMA PET considered superior to choline PET.[58] However, comparing tracers and studies is difficult for a number of reasons, which include heterogeneity of cohorts, different reference standards used, some investigations using tracers combined with CT but others with MRI, and many studies lacking histological correlation of imaging findings.[59] Although PSMA PET is being used widely and appears more accurate to others available,[58] neither PSMA PET nor choline PET detects all metastatic lesions.[58,60]

Conclusion

The mode of diagnosis of prostate cancer is changing, with imaging increasingly establishing an important role in both diagnosis and staging. Prostate MRI has the potential to increase detection of clinically significant prostate cancers and, concurrently, also decrease identification of clinically insignificant low-risk prostate tumours, if biopsies are not performed on patients with normal MRI findings. However, MRI is expensive with investment in ever-improving hardware, post-processing software, together with upskilling of radiologists and urologists interpreting MRI images, requiring consideration in integrating MRI into the prostate cancer diagnostic algorithm. As a consequence, since the majority of men with an elevated PSA will not have prostate cancer detected with biopsies, the need for inexpensive and better triaging tests is more relevant than ever before, so that MRI can be reserved for those with a high risk of malignancy warranting treatment. However, the combination of triaging tests and imaging will increasingly aid urologists in their decision to pursue a diagnosis. Despite these advances, the most important decision remains: "Will the patient in front of me benefit from diagnosis and treatment?" A reflection back to the Hippocratic oath of 'first do no harm' can often aid in this decision.

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ADVANCES IN THE IMAGING OF THE PROSTATE IN THE SETTING OF ELEVATED PSA LEVELS

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Abstract

Mirroring exciting advances in the treatment of prostate cancer, advanced imaging techniques are providing improved detection and staging of this disease. Whereas treatment decisions were previously often made on the basis of probability, more sensitive and specific localisation of disease sites will allow choices that are better tailored to an individual patient's disease. Multi-parametric MRI and PET/CT, particularly using ligands of the prostate specific membrane antigen receptor, provide improved assessment of the prostate and, in the post-treatment setting, prostate bed and of nodal and distant metastatic disease both prior to definitive treatment of high-risk cases and at PSA failure following definitive treatment of the prostate. PET/CT may also help to select patients for targeted therapies based on prostate specific membrane antigen receptor expression, including emerging radionuclide therapy approaches. As well as localising disease sites, molecular imaging also provides opportunities to better characterise and predict biological behaviour and therapeutic response than current imaging techniques. However, despite great enthusiasm and rapid adoption of these techniques in clinical practice, there is a pressing need to better define their role in selecting, planning and monitoring treatment through further, well designed and validated studies.

Background

Management of prostate cancer is being revolutionised by a range of new therapeutic options, as detailed elsewhere in this Forum. Unfortunately, conventional staging is rather insensitive for other than advanced disease, limiting the precise application of these treatments. Conventional imaging with CT and, to some extent, whole-body bone scan also lacks the ability to characterise disease biology, which can have very significant prognostic implications and be vital in determining the need for and timing of active treatment. While the prostate specific antigen (PSA) is a sensitive biomarker of disease, it doesn't provide information about the location of disease and only limited information about the burden of tumour.

When prostate cancer is suspected, diagnosis has relied on ultrasound-guided biopsy but false-negative results occur.[1] Once the diagnosis of prostate cancer has been made, the choice between active surveillance, radical surgery, brachytherapy, external beam radiotherapy and systemic therapies has been fraught with difficulty due to challenges associated with defining the extent of tumour. CT has limited accuracy for T-staging and N-staging due to low soft tissue contrast and the similar radiologic appearances of normal and involved nodes. CT also has significant limitations for M-staging, particularly with respect to the specificity of sclerotic bone lesions. Whole body bone scanning has higher accuracy than CT for bone disease, but provides no information with respect to soft tissue involvement. Tomographic imaging combined with CT has improved the accuracy of diagnosis of bone involvement in prostate cancer, but it still remains suboptimal.[2]

Despite an increasingly conservative approach to management of primary prostate cancer, more aggressive treatment of high-risk and oligometastatic disease is also being pursued. Thus, when deciding on treatment, there is clearly need for imaging technologies that provide both more accurate non-invasive staging and improved characterisation of disease biology, whether at initial diagnosis or biochemical relapse. In this review, advances in imaging that may address these needs will be discussed.

The role of advanced imaging techniques in primary staging

Compared to ultrasound-guided biopsy, MRI-guided biopsy has been shown to be more accurate.[3] This technique can use 'cognitive guidance,' 'software fusion' with ultrasound or 'in-bore biopsy,' with the

latter having the highest positive yield.[4,5] The limited availability and cost of MRI has restricted its use for this purpose in Australia. Multi-parametric MRI (mpMRI) is however, becoming widely used for primary staging of known prostate cancer despite a current lack of reimbursement. This technique has been recommended by the European Society of Urogenital Radiology, which has described a structured system for reporting termed the Prostate Imaging and Reporting and Data System (PI-RADS), denoting the likelihood of significant cancer in a lesion based on a combination of findings on T2, diffusion-weighted (DWI), and dynamic contrast enhanced (DCE) imaging.[6] An updated version, developed in collaboration with the American College of Radiology (PI-RADS version 2) has been in use since the end of 2014 [www.acr.org/Quality-Safety/Resources/PIRADS].

T2-weighted images provide the best anatomical detail of the prostate with cancer foci appearing as areas of low signal intensity. T2 imaging has been acknowledged in PIRADS V2 as the determinant sequence in diagnosis of cancer involving the transition zone. DWI with generation of apparent diffusion coefficient maps is indicative of cellular density of a tumour and correlates with the aggressiveness of prostate cancer and Gleason score.[7] PIRADS V2 recognises DWI as the determinant MR sequence in peripheral zone cancer. DCE MRI assesses angiogenesis but delivers little cost-benefit.[8,9] Spectroscopy can also provide complementary information to DWI but it is not routinely performed due to technical challenges.[10] A pooled study of 14 mpMRI studies (1785 patients) showed an overall sensitivity of 0.78 and specificity of 0.79 for prostate cancer detection with more accurate results in studies with correct use of PI-RADS in studies using less strict criteria.[11] The enhanced soft tissue contrast of T2-weighted MRI compared to CT improves detection of regional nodal involvement but is still limited by size criteria that fail to correctly classify normal size nodes involved by tumour or enlarged nodes that are reactive.[12] Apparent diffusion coefficient measurement can help to increase the specificity for nodal involvement but remains inaccurate for small or necrotic nodes. Contrast agents with specific uptake in lymph nodes increase the sensitivity for nodal involvement but are not approved for use in Australia.[13]

Advanced prostate cancer that has spread beyond the prostate is increasingly being considered for multimodal therapy including local surgery, external beam radiotherapy, androgen deprivation and chemotherapy. This approach is however, controversial and not strongly supported by evidence.[14] The ability to more accurately determine the presence, location and burden of metastatic disease at baseline diagnosis would almost certainly aid stratification within randomised control trials to address this controversy. Whole-body DWI may be a useful technique for evaluating subsequent therapeutic response of bone lesions due to a lack of the 'flare' response seen on bone scanning.[15] The long acquisition protocols currently required for mpMRI of the pelvis combined with body DWI makes this a costly investigation.

PET has also been evaluated as a modality for primary staging of prostate cancer because of its relatively rapid whole-body screening capability. F-18 fluoro-deoxyglucose (FDG) PET yielded discouragingly low sensitivity for disease detection in patients with known metastatic disease on conventional imaging.[16,17] This encouraged development of PET radiotracers with higher affinity for prostate cancer. C-11 choline was one of the earliest.[18] Preliminary studies with stand-alone PET confirmed its utility for N-staging.[19] Subsequently, hybrid PET/CT provided greater opportunity for localising the primary tumour with superior yield demonstrated compared to trans-rectal biopsy.[20] High-grade prostate intraepithelial neoplasia was the most common cause of false-positive uptake.[21] Studies comparing C-11 choline and multi-parametric MRI have yielded conflicting information with respect to relative accuracy, and therefore a combination of these technologies has been recommended.[22-25] Unfortunately, despite being licenced for use in several countries in Europe, C-11 choline is an impractical radioisotope for routine clinical use due to rapid radioactive decay and is not approved or funded in Australia. The logistic limitations of C-11 stimulated development of fluorinated choline analogues.[26] Our own preliminary study demonstrated that both F-18 fluoromethylcholine (FCH) PET/CT and FDG-PET/CT were more sensitive than conventional staging, but FCH PET/CT provided the highest lesion sensitivity.[27] Other fluorinated tracers are also continuing clinical trial evaluation.[28]

Tracers directed against prostate specific membrane antigen (PSMA) represent an exciting development with significantly higher sensitivity than FCH PET/CT and a high diagnostic yield, even in the setting of low level PSA relapse.[29-31] A recent Australian publication comparing PSMA and FCH PET/CT in 38 patients supports this finding.[32] Our own experience in over 500 patients suggests that this is a highly sensitive and specific imaging agent, even in patients with low PSA levels. Despite the advantages of generator production of Ga-68 rather than requirement for a cyclotron, the rapid decay of this radionuclide also poses significant logistical challenges. PSMA-binding agents using F-18,[33] Y-86 and Zr-89 (in the form of an immunoconjugate) also look promising.[34,35]

Whilst FDG PET/CT is insensitive in patients with indolent prostate cancers, there is evidence that it can provide powerful prognostic information by reflecting tumour grade.[36] Through identifying patients with more aggressive disease, it might enable selection of patients most likely to respond to and benefit from chemotherapy.

Evaluation of PSA or clinical relapse after radical treatment

PSA measurement enables early detection of treatment failure following radical treatment of primary prostate cancer. However, it is recommended that contrast-enhanced CT and whole-body bone scanning should only be performed in high-risk prostate cancer in order to optimise the yield with respect to positive studies while ensuring that few men with bone metastases are denied appropriate staging.[37] When patients are found to have persistent or rising PSA levels after definitive treatment, these imaging modalities are often performed without availability of prior baseline studies. If negative, as will be the case in the majority of such patients, local salvage treatment is often contemplated whereas, if localised regional nodal enlargement or a limited number of metastatic sites are identified, more aggressive local salvage therapies, including nodal dissection, wide-field external beam radiotherapy and stereotactic ablative body radiotherapy, are more often being considered. Although supported by only low-level evidence,[38] in selected patients, these salvage treatments directed to nodal recurrence can achieve acceptable oncologic outcomes and may delay the time to systemic treatment with an acceptable safety profile.[39,40] While the patterns of failure have prognostic implications,[41] the evidence base supporting these treatments is compromised by the inability of current imaging techniques to define the true extent of disease.

Assessment of potential residual or recurrent local disease is compromised by post-surgical changes on MRI and by urinary excretion of many of the tracers used for PET/CT. Nevertheless, most of the existing data supporting the use of advanced prostate imaging techniques have been generated in such patients. C-11 choline PET/CT has particular advantages for detecting local recurrence in the setting of prior prostatectomy due to low urinary clearance, but is also more sensitive for nodal and distant metastatic than CT.[42] Early dynamic imaging of the pelvis using F-18 FCH, prior to appearance of activity in the bladder, can improve detection of local tumour recurrence. Delayed whole-body imaging also has good sensitivity for nodal and distant disease.[43]

PET/CT using PSMA ligands might also be helpful for planning salvage nodal dissection.[44] A recent report has confirmed a high yield of Ga-68 PSMA-binding ligands in the restaging setting.[45] The specificity and sensitivity of PSMA PET, combined with the anatomical detail provided by MRI may be an ideal application for hybrid PET-MRI systems.[46]

Conclusion

Those treating prostate cancer clearly need better imaging tests to select, guide and monitor the effectiveness of therapy. In the restaging setting, imaging is an important complementary tool to assess elevated PSA levels. CT and bone scanning have insufficient sensitivity or specificity for disease detection, encouraging widespread adoption of advanced imaging techniques. This is even in the absence of a robust evidence base to support their use and despite lack of reimbursement. MRI is now used for biopsy guidance and even more widely for primary staging or for the evaluation of PSA relapse. Where available, FDG PET/CT has found a limited role in assessing high-grade disease. However, the most promising developments have been in molecular imaging techniques that offer both high sensitivity and specificity. In particular, PSMA PET/CT is being rapidly adopted. Our early experience suggests this is a major advance, but further research is required to define how to use this information to guide and monitor management. Further, PSMA ligands provide options for therapy based on the distribution of disease identified by PET/CT as an example of theranostics [47].

We live in exciting times with respect to both the diagnosis and treatment of prostate cancer.

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ROBOTIC ASSISTED RADICAL PROSTATECTOMY VERSUS OPEN RETROPUBIC RADICAL PROSTATECTOMY: WHERE DO WE STAND IN 2015?

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Abstract

Robotic assisted radical prostatectomy has emerged as the dominant surgical technique for the management of localised prostate cancer in many Western countries. Yet the evidence to support such a radical change in surgical technique has been limited and of poor quality, with the driver of the change initially being aggressive marketing, followed by hospital and urologist competition, and lastly by patients themselves who perceive robotic assisted radical prostatectomy to be the better technique. A critical review of the contemporary literature would suggest that robotic assisted radical prostatectomy may indeed have benefits over traditional open surgery in the areas of length of inpatient stay, perioperative complications and transfusion rates. However, the important parameters of cancer control, continence and potency outcomes appear largely equivalent between the techniques and more determined by surgeon and hospital experience, and patient characteristics, with the advantages of robotic surgery coming at increased cost. There is no question that robotic assisted radical prostatectomy is already widely disseminated and this trend is irreversible regardless of the outcomes of future studies. This however, does pose challenges regarding training in centres that do not have access to robotic technology, credentialing requirements for transitioning open surgeons and maintenance of open skills where robotic assisted radical prostatectomy cannot be performed.

Robotic assisted radical prostatectomy (RARP) has become the surgical method of choice of urologists in many developed nations, in preference to an open radical prostatectomy (ORP). Since the introduction of robotic surgery over a decade ago, the debate over which is the 'best' technique has waged and been the topic of debates in many urology conferences around the world. Yet the level of evidence to support superiority between techniques is poor, with no randomised controlled trials of note to date.[1,2] Most studies have been level 4 data, namely retrospective single centre case series, often comparing a contemporary series of RARP to historical ORP data. In fact, a systematic review of the literature in 2010 demonstrated that 12 authors contributed to writing 72% of published studies.[2] Population data and meta-analyses since then have been valuable, but again do not replace a well conducted randomised control trial as much of the data is incomplete, surgical skill and experience is unstated, surgeon and hospital volumes are often unknown and there is no standardised reporting of complications, nor analysis of pathological outcomes by central pathology review. All these highlight the poor quality of data we have to date and why we look forward with considerable interest to the results of the randomised control trials being performed in Brisbane, Australia, currently comparing the techniques, within the same time period, with the same care pathways, in the same institution, with central pathology review and with experienced urologists performing the surgery.[3] This together with another prospective contemporary but non-randomised trial happening in Melbourne, Australia, will add a lot of knowledge regarding the true benefits of one technique over the other.

Oncological outcomes

Given the fact that a radical prostatectomy is essentially the same operation regardless of technique used, it

seems that oncological outcomes should be similar or identical, and driven more by tumour and surgeon factors. Due to the long lead time to identify differences in cause specific survival or even prostate specific antigen (PSA) free survival, positive surgical margins have been used as a surrogate for surgical quality. Naturally, this is also affected by factors such as pre-operative PSA, tumour volume, surgeon skill and experience, pathological processing and techniques, hospital volume and experience. As such, unless these factors are standardised, the results of comparisons between techniques may be flawed.

A recent meta-analysis demonstrated non-significant differences on the pT2 (p=0.31) margin rates, or overall margin rate (p=0.19), between techniques and no differences in seven year biochemical free survival (p=0.56).[4] This was supported by a meta-analysis of 286,000 radical prostatectomy cases from over 400 published papers, which demonstrated that overall and pT2 positive surgical margin rates were lower in RARP vs ORP (overall 24.2 vs 16.2%; pT2 16.2 vs 10.7%), however following propensity adjustment these differences were not statistically different. A study from the Mayo Clinic controlling for factors such as hospital, pathology and surgeon skill and experience, found no difference in positive margin rate, with RARP having a 15.6% margin rate to 17% with ORP (p=0.608), with no difference in long-term disease biochemical progression rate.[5] This is supported by data from a single centre in Belgium, with RARP having a 30% positive margin rate compared to 21% with ORP (p=.204),[6] from the Health Professionals Follow-up Study (24.5% vs 23.1% p=0.51),[7] from Johns Hopkins (34.3% vs 29.4%, P=0.52),[8] and from Memorial Sloan Kettering (15% each), all comparisons quoted being non-significant.[9] In the latter two studies no difference was noted in biochemical free survival between techniques (p=0.6),[8,9] although at Memorial Sloan Kettering they importantly noted a greater difference of biochemical free survival between surgeons (2.3% crude difference over two years) using the same technique rather than between techniques (0.8% crude difference over two years).[9] They concluded that the surgical approach should be based on the skill and confidence of the surgeon rather than being focused on a specific technique. Case volume appears to be a major factor, with a recent series demonstrating a positive surgical margin rate of 36% in the first 50 case RARP experience to 7.5% in case numbers 251-450.[10] Another demonstrated it required a case experience of more than 1600 cases to obtain a margin rate <10%.[11] This fact would apply equally to both ORP and RARP.

Some multi-institutional studies however, have shown some benefit for RARP over ORP with regards to margins (22.8% vs 13.8%).[12] However, ORP patients had higher risk prostate cancer at the time of this surgical series and were operated on earlier in the study time period, introducing some selection bias. Logistic regression to attempt to correct for these factors demonstrated an odds ratio of 0.76 in favour of robotic surgery (p<0.001). Surgical and hospital case volume and experience were uncertain, and pathological processes likely to be vastly different between centres with no central review. Similar concerns can be raised regarding a recent analysis of the SEER data, comprising 5556 RARP cases, 7878 ORP cases, but critically with nearly 9000 cases excluded from the analysis.[13] ORP once again had higher pre-operative PSA levels and higher clinical stages, and there was no standardisation of pathology processes. RARP was associated with fewer positive margins (13.6% vs 18.3%), mostly in the intermediate and high risk cases. RARP was also associated with less use of additional cancer therapies within six months of surgery (4.5% vs 6.2%), but there was no information about PSA relapse rates, nor cause specific survivals, and hence uncertainty about why these secondary therapies were introduced.

A well-designed prospective, controlled, non-randomised trial (LAPPRO) from Sweden, established that the incidence of positive surgical margins did not differ significantly between groups (21.8% vs 20.9%).[14] However, the population-based Prostate Cancer Registry in Victoria, Australia, in an analysis of 2385 radical prostatectomies over a five-year period, reported a 31% lower PSM rate (p=0.002) in a multivariable analysis comparing RARP with ORP. Patients experiencing a PSM in this series had a greater than five times risk of receiving additional cancer therapy over the following 12 month period. However, this series could not control for patient factors such as clinical stage and surgeon factors such as experience. Training biases may also have contributed to these results, with the bulk of the RARP cases being performed by expert surgeons in the private sector, compared to most ORP being performed by training surgeons under supervision in public hospitals.[15]

The bulk of the literature would suggest that oncological outcomes with regards to surgical margins, biochemical evidence of recurrence and additional therapies are equivalent, with any differences likely to be attributable to factors such as tumour volume, pathology and surgical case volume and experience.

Incontinence

Stress urinary incontinence is one of the more feared complications from radical prostatectomy. Studies are hampered by lack of consistent definitions of incontinence, and the failure to use patient reported outcomes and validated instruments in describing incidence and severity of this complication. Once again, the lack of consistency in regards to matching surgeon skill and experience also makes the interpretation of the data that exist problematic. Most studies appear to demonstrate equivalence when the surgery is performed by skilled surgeons. At the Mayo Clinic, using a

definition of no pads at all as continent, RARP achieved 81.6% continence vs 88% with retropubic radical prostatectomy, which was not statistically significant. Defined as no pads or one security pad only, it was 91.8% versus 93.7%.[5] Further studies using the EPIC-26 questionnaire demonstrated identical scores for RARP and ORP for urinary incontinence (p=0.93).[7] The LAPPRO study also failed to show significant difference between techniques, with 21.3% of men undergoing RARP incontinent versus 20.2% after ORP.[14]

A recent meta-analysis however, was based on nine studies comparing RARP with ORP (mostly historical controls), and demonstrated a mean no pad incontinence rate of 16%.[16] The authors did conclude that RARP achieved better continence rates compared to ORP (92.5% vs 88.7%), with some studies in the analysis demonstrating a faster return to continence with the robotic approach. However, they concluded that age, body mass index, comorbidity index, prior lower urinary tract symptoms and prostate volume were significant pre-operative predictors of urinary incontinence, which naturally were not controlled in any of these comparative studies, let alone with reference to surgeon experience. The authors concluded that multiple design and methodological factors needed to be considered when interpreting these outcomes.

Erectile dysfunction

Erectile dysfunction is another common complication after radical prostatectomy, but studies are again hampered by lack of standard definitions and the lack of use of patient reported outcomes via validated instruments. It has been well shown that erectile dysfunction can also be effected by the ability to nerve spare at radical prostatectomy, age, pre-existing erectile function and co-morbidities. Very few studies have adequately controlled for these factors, nor do they take into account surgeon experience or skill. Data from the Mayo Clinic demonstrated no significant difference between techniques (70% RARP vs 62.8% ORP p=0.08),[5] with results from the Health Professionals Follow Up Study showing no difference in EPIC-26 scores (p=0.66).[7] In the LAPPRO study, erectile dysfunction was found in 70.5% after RARP, and 74.7% after ORP, which was modestly beneficial for RARP with an adjusted OR of 0.81 (95% CI 0.66-0.98),[14] even taking into account factors as mentioned above. Importantly, 40% of patients were not potent pre-operatively, were not interested in sexual activities or did not have nerve sparing for oncological reasons. Of the remaining patients, the three, six and 12 month potency recovery rates were 10%, 53% and 82% respectively, with median time to potency of six months.

A recent systematic review looked at six studies comparing RARP to ORP.[17] Age, baseline potency status, co-morbidities index, and extent of nerve sparing were the most important predictive factors, however an advantage was found in favour of RARP based on seven studies all of level three or four evidence. The authors concluded that 47.8% after ORP had erectile dysfunction compared to 24.2% after RARP, however other factors might have contributed to these discrepancies. Overall, most studies demonstrate modest improvement in potency rates with RARP, although other factors may have played a role when interpreting these results.

Blood loss and transfusion rates

RARP has an advantage in relation to blood loss and transfusion requirements due to the higher intraperitoneal pressure and steep head down position of the patient, thus reducing venous blood loss intra-operatively. Accurate measurements of blood loss, and non-standardised protocols regarding indicators for transfusion, hamper these analyses, however the results consistently demonstrate an advantage of RARP over ORP. Mayo data demonstrated a 13.1% transfusion rate in ORP vs 5.1% in RARP group (p<0.001),[5] and the Health Professionals Follow Up Study with ORP 30.3% vs RARP 4.3% (p<0.001).[7] The investigators estimated on average, 495mL less blood loss with RARP, however they noted that the ORP group was demonstrating a 66 mL/year reduced estimated blood loss, while the RARP cohort was not, indicating that one can no longer compare RARP to historical ORP controls. A systematic review also indicated a 580mL reduced estimated blood loss with RARP, but analysis of the trials included showed huge variability in transfusion rates with ORP, with some series as low as 2-3% of cases, suggesting that case selection, as well as surgeon and hospital experience, may be factors.[4] Another recent systematic review comparing RARP to historical ORP controls demonstrated an advantage to RARP (12.5% vs 1.8%),[18] as well as an analysis of the Nationwide Inpatient Sample (7.7% vs 2.4%).[19] The difficulty in interpreting these data is that the RARP patients had fewer co-morbidities and were more likely to have surgery performed in urban high-volume academic institutions, which may have introduced selection bias. Overall the weight of evidence would suggest a reduced blood loss and transfusion rate with RARP, however the extent of this remains unclear given methodological issues with the studies performed. Contemporary transfusion rates are now low regardless of technique with the gap between techniques appearing to narrow.

Pain/length of stay/peri-operative complications

The suggestion has been made that as RARP offers smaller incisions, this should result in less postoperative pain, and a more rapid return to normal activities. This scenario needs to be compared to a single lower abdominal muscle splitting incision, which traditionally has been a procedure with relatively low pain levels. However, formal studies on analgesic requirements and return to full activities remain sparse in the literature.

Webster et al found that beyond day one, there were no significant differences in pain levels,[20] findings substantiated by Wood et al.[21] A further study did demonstrate minor reductions in morphine sulphate equivalents, with less post-operative analgesic use with RARP, with 28.9% of ORP requiring a single post-operative analgesic refill vs 20.2% of RARP patients.[22] With regard to return to activities, there are no good quality studies comparing RARP and ORP. A study comparing pure laparoscopic RP to ORP, examining quality of life at six weeks, demonstrated a one week advantage in quality of life and return to activities of RARP over ORP, but failed to take into account crucial factors such as activity levels and co-morbidities pre-operatively, nor type of work engaged in by the patient, all of which could have affected the outcomes.[23]

Meta-analyses have consistently confirmed reduced peri-operative complications in patients undergoing RARP owing to the laparoscopic approach, but again uncontrolled for surgical and institutional experience. These include readmission, re-operation, pneumonia, deep vein thrombosis, wound complications and anastomotic leak.[18,19] Furthermore, the urethro-vesical anastomotic stricture rate is significantly reduced with this, sometimes troubling complication, almost eliminated in robotic series where the suturing is completed under direct vision.

Length of stay (LOS) was consistently shorter in the RARP group compared to ORP by approximately one day in most series. In the European series, a reduction from 4.1 to 3.3 days was seen (P<0.001), while in the US Nationwide Inpatient Sample, a prolonged LOS greater than two days was seen in only 14.5% of RARP patients compared to 39.6% of ORP patients (p<0.001).[19] In an academic setting however, a prolonged LOS greater than two days was found in 10.8% of RARP patients compared to 12.6% of ORP, demonstrating that surgical and centre caseload is likely to have an effect in mitigating some of this observed LOS discrepancy.[5] In Australia, the data are more pronounced where LOS with open surgery still remains at greater levels (at least two days), but may reflect lack of adoption of protocols, anaesthetic and pain pathways that are dated and, preoperative counselling.

Cost

All series demonstrate higher costs associated with RARP. A study from the US calculated that RARP was associated with a higher median direct cost of $2315 over ORP, mostly due to surgical supply costs and time in the operating room. If one considered the purchase and maintenance costs, the burden would increase by a further $2698 per patient to an overall increased cost of just over $5000 per patient, based on a centre that performs 126 cases per year.[25] These figures are supported by data from the National Inpatient Sample that demonstrated $2542 higher direct costs with RARP, not including purchase or maintenance costs.[26]

Training in radical prostatectomy

Surgical training in Australia has traditionally followed a master-apprentice relationship, whereby the trainee is given greater responsibility in surgical cases as they gain experience under the watchful eye of the more experienced surgeon. In Australia, data has emerged from Victoria for ORP, where it was concluded that the value of high-volume and fellowship-trained urologists in performing and teaching ORP was a key factor in patient outcomes.[27] There is no such data for RARP, and indeed with only a select few public institutions offering RARP, the role of long-term fellowships cannot be underscored. At present, trainees must assist surgeons in the private sector, which is helpful but does not allow the graduation to an independent surgeon easily. Mini-fellowships and mentoring help in some respects, but a drop in key indicators by surgeons switching to RARP from open, or whom have had little training, is generally accepted as part of a long 'learning curve' of any new technique. In the future, as outcomes are increasingly scrutinised with audits, the best strategy for clinicians to maintain standards and optimal patient outcomes is to understand these elements and direct trainees to appropriate centres for training and fellowships.

Conclusion

While we await the results of the only randomised control trials to have been performed comparing RARP and ORP, we can conclude that RARP is a well-established operation, which gives excellent results in experienced hands, as does ORP. While the important long-term oncologic and functional results appear to remain largely surgeon dependent, for a given surgeon RARP will offer at least equivalent results, with a reduction in peri-operative complications and bladder neck stricture rates. RARP does appear to carry a small (and possibly narrowing) advantage with regards to LOS and transfusion rates, but at an increased cost. Trials to date are often subject to substantial selection bias influencing outcomes, and making conclusions hard to interpret. Nonetheless, an entire generation of trainees in the US have now been trained in RARP, with subsequent de-skilling in ORP. This raises some serious issues for future surgical planning, namely how to train when institutions do not have access to a robot, how does one credential an existing open surgeon transitioning to robotics and how does one maintain open skills in this procedure for those rare occasions where RARP may not be possible for anatomical or mechanical reasons.

It is perhaps time to put this debate to rest and accept that each surgeon should choose their preferred method of performing radical prostatectomy, without the claims from companies, hospitals and urologists that one technique is vastly superior to the other. As demonstrated by the team at Memorial Sloan Kettering,

there was more variability between surgeons using the same technique then between techniques themselves.

While it is entirely appropriate to train new surgeons in robotic technology, it is important that benefits of RARP over ORP are not over-stated and that experienced surgeons in ORP should feel comfortable continuing to offer their preferred operation. A recent study of this transitioning process in an experienced open surgeon demonstrated that it required 99 RARP cases to reach previous ORP levels in regards to sexual function, 182 cases for incontinence and 200 cases with regards to margins, with up to 700 cases to plateau outcomes.[28] This then translates to several, and in some circumstances many years of patients being subjected to a worse functional and oncological outcome should these open surgeons transition. Indeed, some experienced open surgeons may never reach what they were achieving with ORP previously, and therefore this issue remains a potential major ethical dilemma as long as this debate continues.

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ROLE OF CYTOREDUCTIVE PROSTATECTOMY IN NON-ORGAN CONFINED PROSTATE CANCER

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Abstract

Prostate cancer is the most common cancer among Australian men. Despite the surrounding controversies, prostate specific antigen screening has resulted in diagnosis being made at a stage in which the cancer is still confined to the prostate in the majority of cases. However, there is still a small subset of men who are not diagnosed until after the cancer has metastasised. Historically, these cases have been managed with androgen deprivation therapy with no role for surgery. However, with data supporting cytoreductive surgery in other cancers such as kidney, breast and ovarian, there is increasing interest in the role of surgery as part of a multimodal approach to men with metastatic prostate cancer. Early data suggest that surgery in this situation is feasible and safe, with encouraging data suggesting an oncological benefit. Randomised trials are underway to establish who might benefit and which strategy should be incorporated. In the meantime, radical prostatectomy in the context of metastatic disease should be considered experimental.

Prostate cancer is the most common newly diagnosed cancer in Australia, accounting for 25% of all new cancers in men.[1] The introduction of prostate-specific antigen (PSA) screening in the late 1980s is largely responsible for the upward trend in incidence, although this trend has reversed in recent years, likely due to negative messaging about PSA testing and the well-known consequences of over-diagnosis. This has also resulted in prostate cancer being commonly detected at a stage at which the cancer is still localised to the prostate. Surgery, radiation therapy and active surveillance may be considered at this stage of disease, with good outcomes overall.[2,3] However, in approximately 7% of cases, the diagnosis is only made after the cancer has spread beyond the prostate and the role of surgery in this group of men is less clear.[4]

Current management for non-organ confined prostate cancer

Non-organ confined prostate cancer has a poor prognosis, with a five year survival rate of 28% compared with 100% in organ-confined disease.[5] Presently, the treatment of choice in non-organ confined prostate cancer is androgen deprivation therapy (ADT).[6] This has been demonstrated in a number of trials to improve overall survival by causing a PSA decline in approximately 90% of patients. However, the efficacy of cancer control tends to be short-lived. Even in the modern era using chemotherapy in addition to ADT, the median time to progression in men presenting with metastatic cancer is less than one year, with median survival less than four years.[7]

Furthermore, ADT is associated with a variety of adverse effects such as hot flushes, sexual dysfunction, osteoporosis, increased fracture risk, anaemia, decreased cognitive function, metabolic syndrome and increased cardiovascular morbidity, all of which have the potential to severely debilitate a man's quality of life. Albeit a rare consequence, the 'flare' phenomenon that may occur at the initiation of treatment has the potential to be life-threatening in men with high-volume metastatic disease.[8]

Potential benefits of cytoreductive prostatectomy

The benefit of cytoreductive surgery has been clearly established when evaluating other sites of cancer such as the breasts, ovaries and kidneys.[9] Regarding prostate cancer specifically, radical prostatectomy (RP) has been historically discouraged on the basis that surgery carries a risk of peri-operative and long-term morbidity and does not offer a definitive cure. Nonetheless, in recent years, the pendulum has begun to swing as a number of publications have supported cytoreductive prostatectomy being offered to men with metastatic disease, aided by the steady replacement of open surgery by minimally invasive techniques that can offer reduced peri-operative surgical risk.

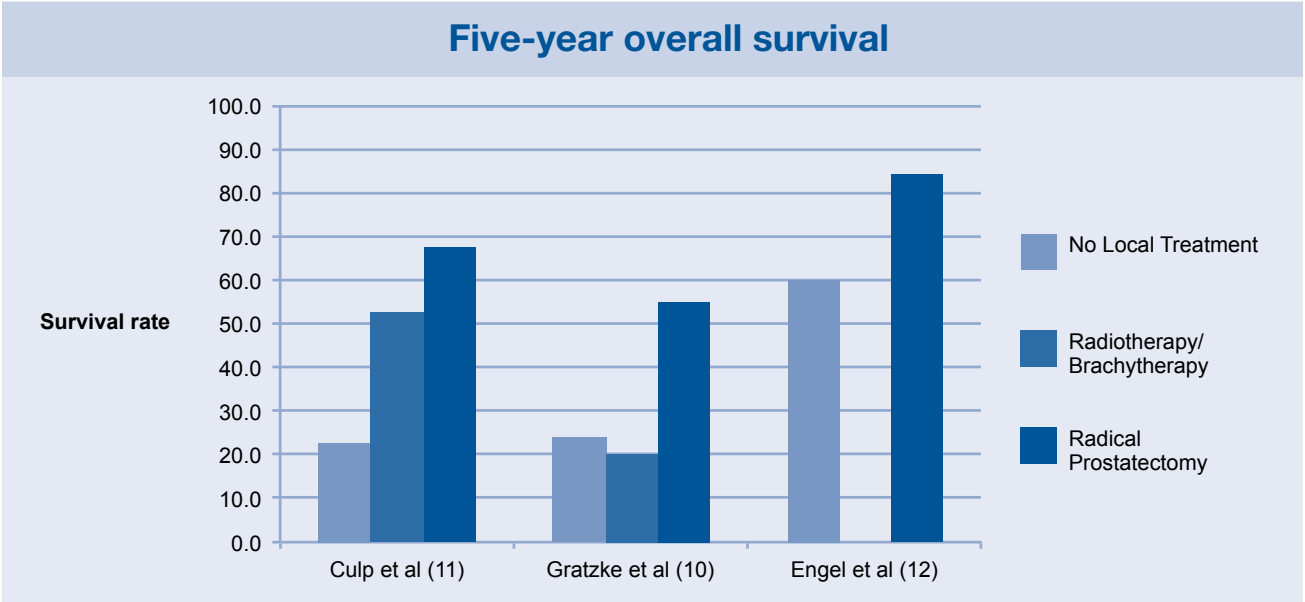
Over the last 10 years especially, results from various studies have suggested an improvement in overall survival and disease specific survival in men with non-organ confined prostate cancer who have undergone surgery to

have their primary tumour removed. Data from the Munich Cancer Registry demonstrated a significantly superior five-year overall survival rate of 55% in patients with metastatic disease undergoing RP, compared with 21% (p<0.01) in the group without surgery.[10] A similar study based on the SEER database containing 8185 men also found superior overall survival rates in the group undergoing RP (67.4%) or brachytherapy (52.6%) compared with the no treatment (22.6%) group (p<0.001) (table and figure 1). The five-year disease-specific survival rates in the same study were analogous to the previous findings, with a significantly higher rate of 75.8% in the men who underwent surgery compared to 61.3% and 48.7% in those who underwent brachytherapy or neither local treatments respectively (p<0.001).[11] These findings are promising for offering surgery to men with metastatic disease.

***Table 1**: Five-year overall survival rates for men with non-organ confined prostate cancer.*

		No local treatment		**Radiotherapy/ brachytherapy**		**Radical prostatectomy**		
	n Total	n	5-year OS	n	5-year OS	n	5-year OS	Comments
Culp et al[11]	8185	7811	22.5	245	52.6	129	67.4	Overall survival and disease specific survival was higher in patients undergoing local therapy of the prostate compared to those undergoing no local treatment. The lack of information regarding ADT is a major limitation given the impact of ADT on prostate cancer progression and survival. No significant difference in cancer-specific mortality was found when comparing BT and radical prostatectomy groups.
Gratzke et al[10]	1538	635	24.0	389	20.5	74	55.0	Significant difference in five-year overall survival (55% vs 21%) in men undergoing radical prostatectomy compared to those who did not.
Engel et al[12]	938	250	60.1	N/A	N/A	688	84.0	Men who had their radical prostatectomy aborted had a higher number of positive lymph nodes and had inferior 10-year overall and relative survival rates. Not undergoing RP was determined to be an independent predictor of decreased survival [hazard ratio: 2.04].

***Figure 1**: Five-year overall survival rates for men with non-organ confined prostate cancer.*



Although the concept of cytoreductive radical prostatectomy is relatively new and has only been explored directly in a small number of studies, there exist other publications that indirectly support this idea. Engel et al reported a greater overall survival of 84% and 64% at five and 10-years respectively in men with prostate cancer who underwent a prostatectomy, despite intraoperative detection of positive lymph nodes. In contrast, those who had their surgery abandoned due to positive nodes displayed rates of 60% and 28% respectively. In multivariate analysis, RP was an independent predictor of survival in this study [hazard ratio 2.04, 95% confidence interval 1.59 to 2.63, p<0.0001].[12] Furthermore, Suardi et al examined men with nodal recurrent prostate cancer on 11C-choline PET/CT, who then underwent salvage lymph node dissection, and reports that 40% of the cohort remained clinical recurrence-free after a median follow-up of 81.1 months.[13] A lack of a control group makes interpretation of this result difficult, but suggests a role of removing tissue where cancer is detectable. Additionally, despite not having a surgical intervention arm, the importance of local treatment to the primary tumour is further highlighted by the reduction in both cancer-specific and overall mortality of 12% and 9.8% respectively in patients who have been managed with both radiotherapy and ADT compared with ADT alone.[14]

Cytoreductive surgery has also been shown to improve the effectiveness of adjuvant treatment. This potential advantage was first reported in studies of metastatic renal cell carcinoma that had a better response to systemic therapy in patients who underwent a nephrectomy than those who did not. In the SWOG 8894 randomised study, Thompson et al saw the same effect in prostatic carcinoma where men who underwent RP prior to ADT experienced a statistically significant decrease in risk of death compared to those who had no prostatectomy [hazard ratio 0.77, 95% confidence interval 0.53 to 0.89].[15] Importantly, the time to castration-resistant prostate cancer was delayed among the group that had undergone prior surgery compared to the men who had not, with a median time of 40 and 29 months respectively.[16] Likewise, newer agents, such as sipuleucel-T, were also more efficacious in patients who have had their prostate removed.[17]

Surgical removal of the primary tumour also decreases patient morbidity and subsequently improves quality of life. Studies of patients with non-organ confined prostate cancer have reported that men who do not have local treatment of their primary cancer tend to develop complications of their urinary tract. Heidenreich et al observed that 28.9% of men who did not receive any local treatment required surgical or percutaneous intervention for local progression of their cancer. Nearly a quarter of this group had a transurethral resection of the prostate for subvesical obstruction and 5.2% required a nephrostomy for hydronephrosis.[16] Surgical management of the primary tumour was most effective in decreasing the rates of local complications, even compared to external beam radiotherapy.[18] Although complications can be treated through various interventions, it is important to consider that these treatments themselves are not risk-free and may negatively impact patient morbidity.[19]

Pathophysiological basis for cytoreductive surgery

The pathophysiological mechanisms behind the conferred benefit of cytoreductive surgery are not fully understood, but different theories have been floated. Kaplan et al proposes that bone marrow-derived haematopoietic progenitor cells play a crucial role in priming the microenvironment of a future metastatic site so that it is more receptive to cancerous cells.[20] Post-colonisation by a cancer cell, growth and cell proliferation is stimulated by endocrine molecules released from the primary tumour site.[21] Hence, it is inferred that by removing the primary tumour progression at a metastatic site would be stunted due to the cells being devoid of the factors necessary for progression.

In a different 'self seeding' hypothesis, it is suggested that circulating tumour cells have the ability to colonise their primary tumour. This can consequently accelerate tumour growth, angiogenesis and stromal recruitment through seed-derived factors causing tumour progression.[22] If this concept were applied, cytoreductive RP would prevent self-seeding and lead to improved survival.

Safety of surgery

Only one relatively small feasibility study has evaluated surgical outcomes of RP in men with metastatic disease, because surgery has not been historically offered as a potential management option in this group. The feasibility study allocated 23 men with biopsy proven prostate cancer with minimal osseous metastases, absence of visceral or extensive metastases and PSA nadir below 1.0ng/mL after neoadjuvant ADT into the intervention group, and 38 men with metastatic prostate cancer who were treated with ADT only into the control arm. This cohort reported a mean surgical time of 127 minutes, blood loss of 355mL, catheterisation time of 5.6 days and hospital stay of 7.8 days. Complications were somewhat higher, as 13% of patients developed lymphoceles that required treatment and 8.6% developed deep vein thomboses. Continence rates of 91.3% were reported using a safety pad definition.[16] This study is however, limited by its retrospective nature, small sample and short follow-up. Thus while the initial results of cytoreductive RP show potential, at present we are mainly restricted to drawing parallels to outcomes of RP in high-risk patients, generally pT3 or greater, in trying to evaluate the safety of surgery aimed at debulking tumour volume in those with metastatic prostate cancer.

Perioperative measures of prostatectomy in clinically advanced cases were comparable to men with organ-confined disease. A review by Yuh et al, examining robotic RP in high-risk patients, reports mean estimated blood loss as 189mL, 168 minutes operative time and complication rates ranging from 3 - 30%.[23] This compares satisfactorily with Novara et al in their review of outcomes in patients of all diseases that reported figures 166mL, 152 minutes and 3 - 26% for identical parameters.[24] Gontero et in a single-surgeon experience, found no significant difference in surgical morbidity between patients of different risk categories, but there was a higher rate of blood transfusions, operative time and lymphoceles in the high-risk patients.[25] The increased incidence of lymphoceles is explained by the high rate of lymph node dissection to more accurately stage the cancer and remove potentially cancerous tissue in patients classified as high-risk, as recommended by the current European Association of Urology guidelines.[6] The rate of lymphoceles in extended lymph node dissections is approximately 3% as reported in a systematic review.[23]

Oncological outcomes for men with high-risk disease undergoing RP are acceptable when contrasted to those men with a lower-grade of prostate cancer. Yee et al reported an overall positive margins rate of 7.4% with subset analysis according to pathological grade, showing positive margins of 3.1% in pT2, 15.9% in pT3 and 55.6% in pT4 disease.[26] Importantly, the abovementioned feasibility study compares favourably with positive margins of 14.3%.[16] The potential to nerve spare is observed by Casey et al, who demonstrated that there was no significant difference in positive margin rates regardless of the extent of nerve-sparing completed in the procedure.[27] This consequently has a positive impact on the man's functional ability.

It is important to consider whether RP in metastatic prostate cancer is feasible in terms of acceptable functional outcomes of continence and potency. A recent systematic review found continence rates ranging from 78% to 95% using a 0-1 safety pad definition in patients undergoing robotic RP.[23] Yee at al reported rates as high as 84% at 12 months using a strict no-pad definition.[26] The aforementioned systematic review also reported potency rates that ranged from 52% to 60%.[23] Additionally, defining high-risk as PSA ≥ 15 ng/mL, ≥cT2b (disease palpable at least bilaterally on digital rectal examination) or Gleason 8-10, Loeb et al reported continence and potency rates of 92% and 62% respectively within 10 years.[28] These figures are comparable to patients with lower-risk disease. Therefore, as is the case with patients with low-risk disease, post-operative continence appears to be markedly less of an issue than potency.

In a comparison of different modes of RP in high-risk patients, there was no significant difference in rates of complications, positive surgical margins or additional therapy between the open and robotic-assisted RP groups. The number of blood transfusions and the length of stay was however, significantly lower in the robotic surgery subset.[29] Thus, it is suggested that while both means of surgery are safe for high-risk patients, robotic-assisted prostatectomy may hold a slight benefit.

Patient selection

Although the aforementioned trials demonstrate that removing the primary tumour is beneficial to the patient, it is important to note that these results are most applicable in only a subgroup of men with certain characteristics. Age ≥70 years, PSA ≥20 ng/mL, high-grade disease and pelvic lymphadenopathy were all determined by Culp et al to act as independent factors that increased cancer-specific mortality. Five-year overall survival and disease-specific survival were greatest in men with one or fewer factors - 77.3% [95% CI, 67.4-84.5] and 89.9% respectively. Patients with two factors showed rates of 53.1% [95% CI, 38.9-65.4] and 68.5%, but these were still superior to those who had neither surgery nor radiotherapy. The subset of men with three or more of the above factors who had their primary cancer treated, showed no significant difference to those who did not. In concordance with other literature, further analysis revealed that patients over 70 years of age, or those with a PSA above 20 ng/mL, were less likely to benefit from local therapy.[11]

Furthermore, it is those patients with a relatively low burden of metastatic disease who are most likely to benefit from this approach. Oligometastatic disease usually refers to patients with five or less sites of recurrent metastatic disease following prior treatment of the primary prostate cancer. There is considerable interest in targeting oligometastatic disease in these cases using ablative techniques such as stereotactic radiotherapy, or extirpative approaches such as salvage pelvic lymph node dissection.[30] However, the definition of oligometastatic disease is contingent of the sensitivity of the imaging used to identify metastases. Conventional imaging such as CT and bone scanning have poor sensitivity and the use of more advanced imaging, such as 68Ga-PSMA PET scanning, will improve selection of patients with truly low volume metastatic disease.[30-32]

Ongoing trials

There are a number of prospective studies currently recruiting which will address the role of radical prostatectomy in men presenting with metastatic disease. These include a randomised study of ADT plus surgery, versus ADT plus radiotherapy, or radiotherapy alone, being run from MD Anderson Cancer Centre (clinicaltrials.gov NCT01751438). Also, a similar study in Ghent is randomising men presenting with metastatic disease to ADT alone versus ADT plus radical prostatectomy (clinicaltrials.gov NCT02138721).

Conclusion

In the context of the recent publications described here, there is increasing interest in the role of RP in select patients with metastatic disease at presentation. These initial results are promising, showing both an improved survival and the potential to delay the time to castration-resistant disease. The surgery itself appears feasible with peri-operative, functional and oncological outcomes being satisfactory compared to other RP data. However, there has only been one study evaluating the safety of cytoreductive RP and as such, most of the parallels have been drawn from men with locally advanced disease. Consequently, further prospective data is required in order establish the role of RP in non-organ confined prostate cancer in selected patients, as part of a multimodal approach.

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WHEN TO CHOOSE RADIOTHERAPY FOR PROSTATE CANCER, AND WHAT TECHNIQUE?

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Abstract

This review describes the present curative role of radiotherapy in men with localised prostate cancer, and the many technical innovations that have occurred over the last 20 years that have improved its accuracy and safety. These have resulted in today's state of the art irradiation technique known as 'imaged guided intensity modulated radiotherapy'. Emerging changes in practice for men with good prognosis tumours, which include radiation dose escalation, and major reductions in the duration of radiotherapy treatment courses are outlined. Finally, the role of adjuvant treatments for men with poor prognosis, high risk locally advanced tumours, and new approaches to these initiatives are summarised.

Choosing curative radiotherapy for prostate cancer

Until the turn of the century, radiotherapy techniques had serious limitations and adverse outcomes, including primary tumour progression and radiation-induced morbidity. Thanks to the technical innovations described below, external beam radiotherapy (EBRT) is now a curative option for all men with newly diagnosed localised prostate cancer, where CT scans of the abdomen and pelvis and whole body isotopic bone scans are negative for metastases. Fortunately, radical prostatectomy has also undergone important technical improvements. The decision the patient has to make is therefore more difficult and the information he and his partner need to receive is more comprehensive. The most obvious reason for this is that the curative options for prostate cancer, their side-effect profiles, and their accessibility and cost profiles are so different. One man can undergo radical surgery, another, a course of radiotherapy and a third can receive androgen suppression therapy (AST) prior to other treatments. A fourth who has a curable cancer can be offered monitoring without treatment (active surveillance). This option is particularly difficult to understand, because most newly diagnosed patients and their partners share the common expectation that all localised cancers 'must' be treated with the intention of cure. Perceptions of the experience, integrity and communication skills of the doctors that may be administering his treatment will usually also be important considerations when choosing treatment type.

For men with good prognosis tumours that fall into the 'low risk category' i.e. T stage 1c 2a, Gleason score (GS) less than or equal to 6 and prostate specific antigen (PSA) ≤10 where metastatic progression within their lifespans is unusual (i.e. <20%), there is little to choose between the oncological outcomes that follow radical prostatectomy, EBRT or brachytherapy and active surveillance. The patient's decision hinges on the types of side-effects he is prepared to risk, knowing that most of them could be permanent (see table 1).

***Table 1**: Side-effect profiles of treatments used in men with low risk cancers. N.B. Radical prostatectomy and EBRT techniques have improved considerably in the last decade. Mature side-effect data are lacking and may differ from the figures presented, which should be considered as being illustrative.*

Side effects	Radical prostatectomy	Radical EBRT	Low dose rate brachytherapy	Active surveillance
Urinary	Incontinence <10%	Urethral strictures <5%	Urethral strictures <15%	None
Rectal	None	Bleeding, frequency and urgency <10%	Bleeding <5%	None
Sexual	Erectile dysfunction >50%	Premature loss of erectile function: age dependant in <60%	Erectile dysfunction <25%	None

For men with intermediate risk cancers i.e. T stage 2b or GS of 7 or PSA 10 - ≤20, where the chances of cancerous progression within their lifespans are moderate (20-40%), the treatment options are restricted to radical prostatectomy and EBRT. Because there is little to choose between these two options from the oncological endpoint perspective, the patient will select treatment largely on the same considerations listed above.

For men with high risk, locally advanced cancers i.e. T stage ≥2c or GS 8-10 or PSA >20, the probability of metastatic cancerous progression within a 10 year period is high (i.e. ≥50%). Unless there are serious intercurrent medical disorders, radiotherapy with neo-adjuvant and/or adjuvant androgen suppression is usually recommended. Further discussion of this approach follows under 'new developments'.

Technical innovations now in common use

The most commonly used technique for delivering curative irradiation is 'image guided intensity modulated radiation therapy,' which employs several important computer driven technical innovations that have taken place in the last 20 years:

1. First is the modern radiotherapy planning computer, which enables three dimensional treatment volumes to be delineated directly upon the patient's CT images. These are often fused with coregistered magnetic resonance, which enables accurate definition of the prostatic apex and allows the internal anatomy of the prostate to be visualised, often including the tumour itself. Modern planning computers make it easy to employ very sophisticated radiation beam arrangements that create uniform dose distributions in irregularly shaped target volumes, while restricting radiation doses to surrounding structures to levels that are well tolerated. Figure 1 shows how radiation dose is built up within the target volume using multiple small shaped beams through 'intensity modulated radiation therapy'.

2. Such sophistication would not be possible without the ability to shape the beam using millimetre thick shielding blades, each moved independently into position by its own computer controlled motor. This equipment is known as a 'multileaf collimator' and the way it shapes the radiation beam is illustrated in figure 2.

3. Verification that each day's treatment beams are accurately directed at the intended target volume is achieved by an 'electronic portal imaging device'. This equipment generates an electronic image similar to those produced by diagnostic x-ray 'image intensifiers', using the linear accelerator's high energy x-ray beam. Because the prostate moves up to two centimetres many times each day, cranio-caudally, radio-opaque (gold grain) fiducial markers are inserted into the prostate prior to radiotherapy. This enables the position of the prostate relative to adjacent structures to be defined using the electronic portal imaging device prior to each treatment for electronic comparison with its position at the time of planning. Skilful treatment couch movements by the staff then enable the beams to pass through the prostate exactly as planned. This process, known as 'image guided radiation therapy' is capable of achieving important reductions in treatment side-effects.[1]

4. Sophisticated beam arrangements are not the only way to achieve large differences in radiation between the target volume and adjacent normal structures. Innovative developments in computerised remote after-loading equipment enable highly radioactive iridium sources to be transferred from safe storage directly into catheters inserted within the prostate. The procedure is known as 'high dose rate brachytherapy' and has been used as a successful treatment of early stage prostate cancer by itself, or as an adjunct to external beam radiotherapy for more advanced localised tumours.[2-4]

Figure 1:
(a) Shows the extent of beam shaping achievable by linear acceleration prior to 2000. Although the banana shaped target volume is well covered, two-thirds of the oval shaped normal tissue structure receives exactly the same dose.
(b) Shows how the multiple small beams used in intensity modulated radiation therapy achieves much lower doses in the oval normal tissue volume, than the banana shaped target volume.

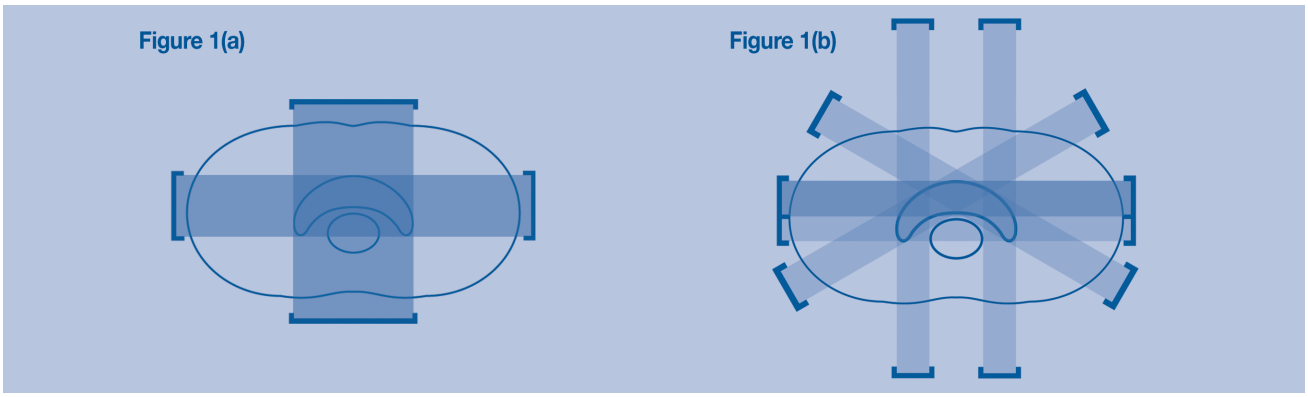
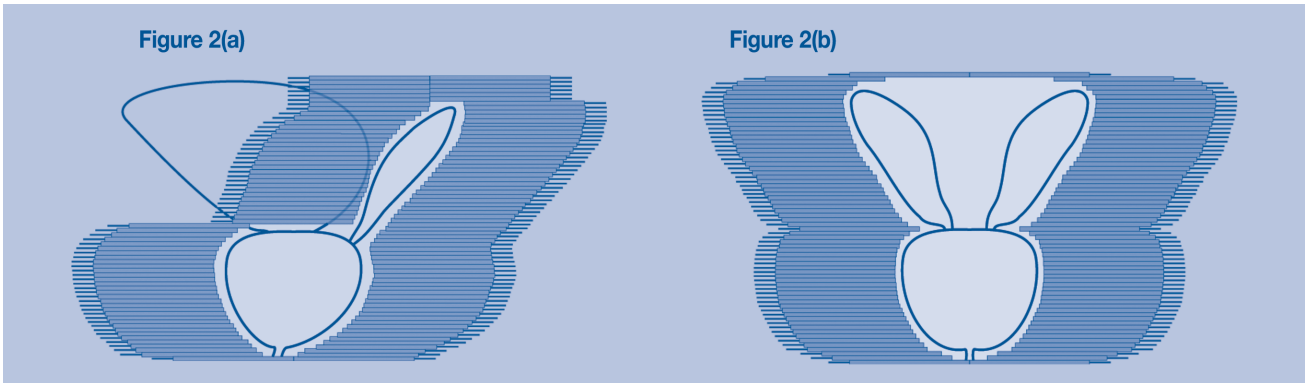


***Figure 2**: Shows how the radiotherapy beam can now be shaped to conformally cover the prostate and seminal vesicles using multi-leaf collimation.*
2(a) from the lateral projection,
2(b) from the antero-posterior projection.



New developments

a) Radiation dose escalation

The technical improvements described above enable higher tumour radiation doses to be delivered without increasing doses to adjacent healthy normal structures. One of the benefits to emerge is an improvement in the curative potential of radiotherapy for localised prostate cancer. This has been demonstrated in a series of randomised 'radiation dose escalation trials' conducted on both sides of the Atlantic.[5-11] The higher doses used in these trials have led to significant reductions in PSA progression. To date, however, only one has demonstrated reductions in metastases and mortality.[12]

As several authors have pointed out, the question arises whether adjuvant androgen suppression is necessary now that higher radiation doses are readily achievable.[13,14] Probably both are necessary for optimal outcomes. However, this conclusion awaits confirmation by the RTOG 0815 trial which is expected to report in late 2015. In the meantime, 2015 results from the analysis of the structured radiation dose escalation program built into the stratification scheme of the 'RADAR' trial run in 23 centres across Australia and New Zealand, are now in press.[4] In this program, EBRT doses used were 66, 70 and 74Gy in 2Gy incremental fractional doses. In centres equipped with HDRB apparatus, it was also permissible to use the option of escalating dose to >80Gy, using 46Gy in 2Gy incremental fractions using EBRT, followed by a HDRB boost in three divided doses over 24 hours. However, improvements are usually bought at a cost. In the RADAR trial there was an increase in dysuria and stream weakness in subjects receiving HDRB boosts. Formal evaluation of these reports indicate that the use of HDRB boosts was associated with urethral strictures.

b) Shortening radiotherapy courses

The realisation that two incremental fractions of 2Gy would kill less prostate cancer cells than a single dose of 4Gy lead to the interesting possibility that a commonly used conventionally fractionated course of 74Gy, using 37 fractions of 2Gy over 7.4 weeks, would not necessarily be more effective than a shorter course of 60Gy using 20 fractions of 3Gy over four weeks, or a very short course of 34Gy using 5 fractions of 6.8Gy over one week.[15] However, these interesting possibilities would not be considered exciting unless these shorter courses were shown to cause similar or lower levels of long-term side-effects.

Sufficient studies using brachytherapy and/or EBRT have follow-up data indicating that this approach is worth pursuing. Randomised trials are now underway to determine what the optimal options will ultimately be. Unfortunately, it could be a decade or more before this initiative translates to the clinic.

c) The use of adjuvant treatment regimens

The veterans trials of adjuvant treatment regimens following prostatectomy in the 1960s showed that the majority of men dying from prostate cancer did so as a result of metastatic spread.[16] However, the development of successful adjuvant regimens did not develop momentum until the advent of luteinising hormone-releasing hormone analogs and anti-androgens in the 1980s provided a means of delivering temporary AST. It quickly became evident that men with high stage, high grade, apparently localised cancers, commonly dubbed 'high risk' or 'locally advanced prostate cancers' (LAPC), had the most to gain from adjuvant regimens in associated curative EBRT.

Over the next 20 years, Radiation Therapy Oncology Group (RTOG), European Organisation for Research into the Treatment of Cancer (EORTC), Trans Tasman Radiation Oncology Group (TROG) and other trials groups were to demonstrate that various durations of AST could more than halve prostate cancer specific mortality (PCSM) and produce clinically relevant improvements in overall survival in men with 'high risk' (localised) cancers. The reduction in metastatic spread was identified as the major contributor to survival improvements. Space precludes description of all of these trials, but table 2 provides their prostate cancer specific mortality and overall survival outcomes.

***Table 2**: Twenty-five years of randomised control trials addressing the value of different durations of adjuvant androgen suppression in the curative management of intermediate and high risk prostate cancers treated by radiotherapy.*

Table 2a. Radiotherapy alone versus short-term neoadjuvant AST (NAST)/radiotherapy

			PCSM			
Trial	**Sample size**	**Duration of AST tested**	**Time**	**Control versus exp % (absolute difference %)**	**HR < 1 PCSM**	**HR > 1 OS**
Predominantly intermediate-risk cancers						
1st Boston	206	0 mths vs 6 mths (NAST)	8 years	11.6 vs 2.4 (9.2)	0.24*	1.79*
RTOG 94.08	1979	0 mths vs 4 mths (NAST)	10 years	8 vs 4 (4)	0.53*	1.17*
Predominantly high-risk cancers						
RTOG 86.10	456	0 mths vs 4 mths (NAST)	8 years	31 vs 23 (8)	0.74*	NS
TROG 96.01	802	0 mths vs 3 mths vs 6 mths (NAST)	10 years	22 vs 18.9 vs 11.4 (10.6)	0.49*	1.59*

Table 2b. Radiotherapy alone versus long-term adjuvant AST plus radiotherapy

			PCSM			
Trial	**Sample size**	**Duration of AST tested**	**Time**	**Control versus exp % (absolute difference %)**	**HR < 1 PCSM**	**HR > 1 OS**
Predominantly very high-risk cancers						
RTOG 85.31	945	0 mths vs indefinite AST	10 years	22 vs 16 (6)	0.59*	1.30*
EORTC 22863	401	0 mths vs 36 mths AST	10 years	30.4 vs 10.3 (20.1)	0.29*	1.96*

Table 2c. Short-term AST plus radiotherapy versus long-term AST plus radiotherapy

			PCSM			
Trial	**Sample size**	**Duration of AST tested**	**Time**	**Control versus exp % (absolute difference %)**	**HR < 1 PCSM**	**HR > 1 OS**
Predominantly very high-risk cancers						
RTOG 92.02	1514	4 mths NAST vs 4 mths NAST + 24 mths adj AST	10 years	16.1 vs 11.3 (4.8)	0.70*	NS
EORTC 22961	940	6 mths adj AST vs 36 mths adj AST	5 years	4.7 vs 3.2 (1.5)	0.58*	1.41*

Abbreviations: 0mths, radiotherapy alone; control, control arm; exp, experimental arm; HR, hazard ratio; Med FU yrs, median follow-up years; Min FU yrs, minimum follow-up years; NS, not significant; OS, overall survival; PCSM, prostate cancer-specific mortality; *significant.

It is important to note that the absolute reductions in mortality, which range between 6% and 20.1%, in trials comparing EBRT alone with EBRT plus AST, are not as impressive as the relative reductions achieved (table 2a and 2b). They are even less impressive in the trials comparing short- and long-term adjuvant AST (i.e. 1.5% at five years and 4.8% at 10 years, in table 2c). These smaller margins of benefit increase the importance of knowing what adverse sequelae occurred in these trials.

d) New adjuvant strategies

Two lines of clinical evidence have influenced the debate concerning the optimal duration of AST and the need for new adjuvant strategies for the treatment of LAPC. First, over the past 15 years, a large number of reports in the international literature have described the prolonged harmful consequences of long-term AST. Aside from the well-known unwanted side-effects,[17] which include loss of libido, erectile dysfunction, gynecomastia and hot flushes, most men also experience some degree of anemia,[18] sarcopenia (muscle loss),[19] and loss of bone mineral density (with increased fracture risk).[20,21] Other commonly occurring phenomena include permanent hypogonadism,[22] some degree of cognitive dysfunction,[23] mood disturbances and depression.[24] Less common problems are exacerbation of 'the metabolic syndrome,'[25] (which includes hypertension, diabetes, hypercholesterolemia, weight gain and increased risk of myocardial infarction.)[26,27]

Second, evidence from two large-scale randomised control trials have shown that indefinite durations of AST by itself achieve limited outcome benefits in LAPC. One was conducted by the Scandinavian Prostate Cancer Group Study and the Swedish Association for Urological Oncology 3,[28] and the other by the National Cancer Institute of Canada-Clinical Trials Group.[29] Both identified limited, but significant improvements in survival by the addition of radiotherapy to long-term AST. This suggests that new therapeutic agents with different modes of action need to be incorporated into adjuvant treatment strategies to achieve better results.

Since most of the longer term complications occur following AST durations greater than two years, two trials have tested the value of 18 months AST plus radiotherapy. The Canadian trial run by Nabid et al compared 18 months with the 36 months AST regimen used by the EORTC (in tables 2b and 2c).[30] Preliminary data indicated that quality of life measures were superior in the 18 month arm, but produced similar oncological outcomes to 36 months. The TROG 03.04 RADAR trial compared 18 months with six months AST in a 2x2 factorial trial, where the second factor was 18 months of zoledronate. Preliminary data indicated that after three years of follow-up, quality of life measures were no different in the six and 18 month AST trial arms.[31] Oncologic endpoints were somewhat better in the 18 months AST trial arm. The influence of zoledronate was unexpected and is described below.

The emergence of drugs with activity against 'castrate resistant' prostate cancer, i.e. prostate cancer that is no longer responsive to androgen suppression therapy, has led to hopes that these agents will improve outcomes in men receiving radiotherapu/AST combinations with curative intent.[32] The bisphosphonates have been the most common class of drugs to be tested in this setting. Clodronate was integrated into British Medical Research Council Prostate 4 and Prostate 5 trials.[32,33] It was found to improve survival in men with metastatic, but not localised prostate cancer and provided strong encouragement for continued evaluation of the more 'oncologically' potent aminobisphosphonates. One of these, zoledronate, was found to have a wide range of anticancer activities in preclinical studies and significant clinical benefits in men experiencing 'skeletal related events' due to prostate cancer.[34,35] Since then, three international trials have gone on to assess the value of zoledronate as an adjuvant treatment and include subjects with LAPC. The TROG 03.04 RADAR trial completed enrolment of 1071 subjects in 2007 and reported preliminary oncological outcomes in 2014. Unexpectedly, evidence of an interaction between the use of zoledronate and the GS of the primary tumour emerged. Of greater interest was the beneficial effect of zoledronate on distant progression outcomes in men with GS 8-10 tumours,[31] which are well known to be the most refractory tumours to AST strategies. A final report is projected to be released in late 2017. The multi-centre European ZEUS trial addressed the effectiveness of four years of three monthly zoledronate for the prevention of bone metastases in high risk prostate cancer patients. It completed recruitment of 1300 patients in 2008 and reported in 2014 that zoledronate did not prevent the development of bone metastases.[36] This finding was regardless of the GS of the primary tumour (personal communication from Prof. Wim Witges 2014). Enrolment to the STAMPEDE (Systemic Therapy for Advancing or Metastatic Prostate Cancer) trial is ongoing, and the number of men with LAPC who will receive the planned 26 months of zoledronate is yet to be reported.

More recently, interest has focused on the cytotoxic agent docetaxel, which has improved survival in heavily pretreated men with advanced castrate resistant prostate cancer.[37,38] The RTOG is evaluating its use in combination with long-term AST, by determining whether its addition to the 28-month AST/RT protocol, successful in the RTOG 92.02 trial,[39] will further improve outcomes. A multi-centre trial run from the Dana Farber Institute, which includes centres from Australia and New Zealand, is determining whether its use will improve on outcomes achieved by six months of AST and radiotheraly.[40] It is unclear when these two trials will report their oncological outcomes.

In summary, the outlook for men with newly diagnosed high-risk LAPC is highly encouraging. Ten year prostate cancer specific mortality rates near 10% are now being achieved using current best practices. It is highly likely that the next generation of trials will bring these rates down to <5%.

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EVOLUTION OF ANDROGEN DEPRIVATION THERAPY

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Abstract

The androgen signalling axis is critical for the development and progression of prostate cancer. Therefore, the mainstay treatments for metastatic disease are hormonal manipulations aimed at reducing androgen levels and/or blocking the androgen receptor, collectively termed androgen deprivation therapy. This review will discuss the evolution of androgen deprivation therapy since it was instigated more than 70 years ago, and outline the key mechanisms underlying its inevitable failure. We will also briefly introduce potential new androgen signalling-targeted therapies in clinical development.

Prostate cancer is the most common cancer and the second most common cause of cancer mortality in men. In Australia alone, there are >21,000 new diagnoses and >3200 deaths per annum.[1] Metastasis to the bone, lymph nodes, lung, liver or brain is primarily responsible for mortality from prostate cancer. Some patients are diagnosed with metastatic disease at their initial evaluation, while others develop metastases after failing primary surgical or radiation therapy.

Huggins and Hodges demonstrated in 1941 that prostate cancer is driven by the male sex steroid hormones, androgens.[2] Androgens are produced through a pathway involving the hypothalamus, pituitary, testes and adrenal glands and mediate their action by binding to the androgen receptor. Both androgens and the androgen receptors are located in almost every body tissue and have distinct roles in each organ.[3] Testosterone is the major circulating androgen, with 90-95% secreted by the testes and 5-10% secreted by the adrenal glands. Almost all circulating testosterone is bound to sex hormone binding globulin, which prevents it from diffusing into cells. After passively entering prostatic epithelial cells, free testosterone is converted to the more potent androgen 5ï-dihydrotestosterone (DHT) through the action of 5ï-reductase. Subsequent binding of DHT by the androgen receptor causes it to move from the cytoplasm to the nucleus of the cell. Once in the nucleus, the androgen receptor binds to DNA and regulates the expression of hundreds to thousands of genes.[4] Genes regulated by the androgen receptor are enriched for those involved in processes like cellular proliferation, differentiation, metabolism and steroid biosynthesis.[4,5] The prototypical androgen-regulated gene is KLK3, which encodes prostate specific antigen (PSA). Induction of PSA expression by enhanced androgen receptor activity in prostate cancer is evidenced by increased serum PSA levels in patients, which is used to diagnose disease and to identify recurrence following therapies.

Castration-sensitive prostate cancer

The androgen axis is the first and primary target for patients with locally-advanced or metastatic castrate-sensitive disease. Hormonal manipulation to decrease circulating androgen levels, commonly referred to as androgen deprivation therapy (ADT), reduces circulating testosterone levels by 90-95%. ADT causes cancer regression and a decrease in serum PSA in the vast majority of men; this therapy-responsive disease state is referred to as castrate-sensitive prostate cancer. An overview of the evolution of ADT for castration-sensitive prostate cancer is outlined below.

Since the primary source of androgens is the testes, surgical castration via removal of the testes (orchiectomy) was initially the intervention of choice. While surgical castration achieves very effective ADT, it is associated with debilitating physical, emotional and psychological side-effects. In the 1960s, 'medical castration' using synthetic estrogens such as diethylstilbestrol (DES) became a common alternative. Although direct beneficial effects of DES in the prostate have been described, DES primarily acts by inhibiting luteinizing-hormone-releasing hormone (LHRH) through negative feedback on the hypothalamic-pituitary axis. DES proved effective in achieving castrate levels of circulating testosterone, and was used therapeutically for a long time, but fell out of favour because it caused cardiovascular complications, including increased rates of mortality from cardiac events.[6]

The 1970s saw the advent of agents that block androgen binding to the androgen receptor, referred to as anti-androgens (figure 1). Anti-androgens can be classified as steroidal (e.g. cyproterone acetate, medroxyprogesterone acetate) and non-steroidal (e.g. flutamide, nilutamide and bicalutamide); the latter are preferable since they preserve potency and libido in most cases.

Long-acting synthetic LHRH agonists became available in the 1980s and, given that they achieved castrate levels of circulating androgens while sparing men surgery and the associated psychological effects, as well as eliminating the use of DES, represented a revolutionary new form of ADT. LHRH agonists such as leuprolide and goserelin are now generally the first-line ADT, being administered subcutaneously in a slow-release form approximately every 3-6 months. LHRH agonists initially activate the pituitary, causing luteinising hormone release and a subsequent rise in androgens. After persistent stimulation, the pituitary becomes desensitised and LHRH receptors are reduced, causing a concomitant decline in serum androgen levels. LHRH agonists target androgen production both in the testes and the adrenals and, like other forms of ADT, cause disease regression in most patients, but for variable lengths of time.[7] The initial rise in androgens driven by luteinising hormone release can cause 'flare' or worsening symptoms of metastatic disease. In these patients, non-steroidal anti-androgens are often administered prior to LHRH agonists to prevent symptomatic flare by inhibiting the action of the androgen receptor.

The imidazole antifungal agent ketoconazole also became available as a treatment of advanced prostate cancer in the 1980s. Ketoconazole exerts its therapeutic effect in prostate cancer primarily by inhibiting the activity of multiple cytochrome P450 enzymes, including CYP17A1.[8] By doing so, ketoconazole inhibits the conversion of cholesterol to pregnenolone and thus suppresses a key step in steroidogenesis, inhibiting testicular, adrenal and intratumoral androgen biosynthesis. Until quite recently (circa 2013), ketaconazole continued to be employed therapeutically with some success to treat advanced prostate cancer.[9,10] However, serious liver toxicity associated with ketoconazole has led to its discontinuation for the treatment of prostate cancer in Australia and most other countries.

Dutasteride is a drug used to treat benign prostatic hyperplasia, an androgen-driven condition characterised by an enlarged prostate.[11] It acts by inhibiting both Type 1 (found throughout most tissues, including skin, liver and prostate) and type 2 (expressed predominantly in prostate and reproductive organs) 5ï-reductases. Given its inhibitory effect on DHT production, dutasteride was assessed for the chemoprevention of prostate cancer in clinical trials in the early 2000s. Despite the observation of a slight overall reduction in prostate cancer incidence in the dutasteride treated group, there was an overall increase in higher grade prostate cancer associated with dutasteride treatment, making dutasteride inappropriate in a chemoprevention setting.[12] A more recent study of dutasteride demonstrated its efficacy in reducing cancer recurrence in an active surveillance cohort of men with low-risk, localised disease, and there was no evidence for it causing more aggressive disease in this cohort (REDEEM study; HR 0·62, 95% CI 0·43–0·89).[13] Given these data, the chemopreventative utility of dutasteride is questionable. However, it could prove more useful in the setting of aggressive disease in combination with other agents; indeed, it is now being tested in combination with abiraterone in a clinical trial (NCT01393730).

Degarelix and other gonadotropin-releasing hormone (GnRH) antagonists have been developed more recently and are alternatives to LHRH agonists and anti-androgens. GnRH antagonists block receptors in the pituitary and result in decreased levels of luteinising hormone, follicle stimulating hormone and testosterone production. A key advantage of GnRH antagonists is that they do not cause flare, while a disadvantage is that they require monthly subcutaneous administration.

The recognition that intra-prostate levels of DHT remain relatively high even in men with castrate levels of circulating testosterone, led to the development of a therapeutic strategy known as combined androgen blockade.[13,14] This approach combines an LHRH agonist or orchiectomy with either a steroidal or a nonsteroidal antiandrogen to block androgens of both adrenal and testicular origin. While initial studies on combined androgen blockade were positive,15 other studies do not support the superiority of this strategy over monotherapy.[15]

Potential side-effects from the aforementioned androgen deprivation therapies include decreased libido, impotence, hot flashes, gynecomastia, breast tenderness, osteoporosis, anemia, weight gain and increased cholesterol. Since these side-effects have a significant impact on the quality of life of men undergoing long-term ADT, there is wide-spread interest in developing selective androgen receptor modulators that abrogate the growth promoting activity of androgens in prostate tumour cells, while maintaining their beneficial effects in other tissues.[16]

Castration-resistant prostate cancer

The vast majority of patients with prostate cancer will initially respond to ADT for a variable period of 2-15 years. However, the ongoing selective pressure placed on prostate cancer cells in an androgen deprived environment drives the development of resistance, after which time the prostate cancer invariably recurs and continued growth ensues, as evidenced by rising PSA levels. At this stage, the disease progresses despite the maintenance of castrate levels of serum testosterone and is referred to as castration-resistant prostate cancer (CRPC).[17]

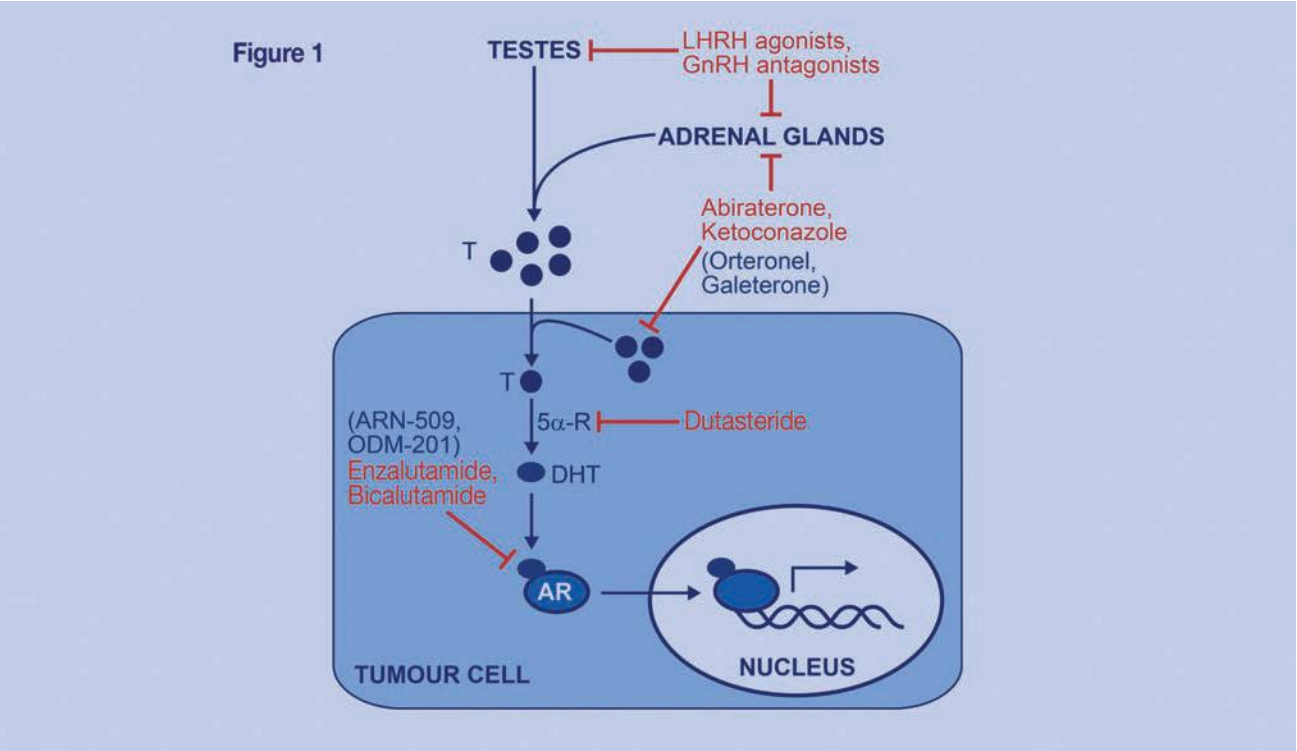
The totality of research over the past decade has revealed that the most common event associated with failure of ADT is the inappropriate activation or

maintenance of androgen signalling.[17] Many androgen signalling-dependent mechanisms have been identified as drivers of the development of castration resistance, most of which involve direct changes to the androgen receptor. First, the androgen receptor is frequently overexpressed in CRPC, often as a result of increased copies of the androgen receptor gene, and this can result in the receptor being activated by castrate levels of androgens ('hypersensitive signalling').[18,19] Second, gain-of-function mutations of the androgen receptor have been reported in a minority of CRPC cases.[20-25] Mutant receptors typically exhibit one of two main phenotypes: increased promiscuity of activation by non-classical ligands (including the conversion of antiandrogens from antagonists to agonists);[26] or greater transactivation capacity via altered interaction with co-regulators.[27,28] Third, deregulation of androgen biosynthesis also contributes to sustained androgen receptor signalling in CRPC. Mechanisms of deregulation include the conversion of non-testicular (i.e. adrenal) androgens or other steroid hormones to more potent androgens in peripheral tissues, including the prostate, and the overexpression of enzymes essential for androgen biosynthesis.[29-31] Thus, serum testosterone levels may not accurately mirror the intraprostatic environment.[32] Fourth, the presence of truncated versions of the androgen receptor that typically lack the majority of the ligand binding domain and are constitutively active proteins, are frequently enriched in CRPC samples and can drive androgen-independent cancer growth in pre-clinical models.[33-37] Importantly, a recent study found that mRNA of the AR-V7 variant predicted lack of response to the androgen signalling inhibitors abiraterone and enzalutamide.[38] Fifth, emerging evidence suggests that inappropriate expression of androgen receptor co-regulators also contributes to the development of castration-resistant disease.[39] We and others have demonstrated that the transcriptional output of androgen signalling is heavily dictated by a complex system comprising over 200 co-regulator proteins,[39] and their expression and function is often altered in response to ADT and during the development and progression of CRPC.[40,41] Lastly, there is extensive interplay between androgen signalling and other growth factor signalling pathways in prostate cancer. This interplay, which often causes changes in the post-translational modifications of the androgen receptor (i.e. phosphorylation, ubiquitylation, acetylation and sumoylation), can stimulate activity of the receptor in the castrate environment.

Improved targeting of the androgen receptor in CRPC

Since 2010, several new drugs have been approved by the Federal Drug Administration, including abiraterone and enzalutamide. These drugs enable more effective inhibition of intra-prostatic androgen production or the androgen receptor itself (figure 1).[42]

***Figure 1**: Current agents (red) and agents in clinical development (blue and in brackets) that target the androgen signalling axis in prostate cancer (5αR, 5αreductase; AR = androgen receptor; DHT = 5αdihydrotestosterone; GnRH, gonadotropin-releasing hormone; LHRH, luteinizing-hormone-releasing hormone; T = testosterone).*



Blocking androgen production

Abiraterone decreases androgen and glucocorticoid production by inhibiting the 17-ï hydroxylase and 17,20-lyase activities of CYP17, a key enzyme involved in androgen synthesis.[43,44] Abiraterone received FDA approval in 2010.[45,46] In the COU-301 study, patients with CRPC treated with abiraterone had longer median overall survival (OS) compared to the placebo group (15.8 months vs 11.2 months; HR 0.74; 95%CI 0.64-0.86). Importantly, abiraterone produced a greater OS benefit for patients than the original (now discontinued) CPY17 inhibitor, ketaconozole (19 months vs 11 months; HR 0.53).[9] Abiraterone toxicity was low, with the most common adverse events being fatigue, anemia, back pain, bone pain and fluid retention or edema. Since the inhibitory effect of abiraterone on both the 17-ï hydroxylase and 17,20-lyase activities of CYP17 results in an accumulation of mineralocorticoids, its administration requires concomitant use of steroids. This side-effect may be minimised with the newer CYP17 inhibitors orteronel (TAK-700) and galeterone (TOK-001), which do not inhibit 17-ï hydroxylase.[47,48] However, orteronel plus prednisone failed to meet the primary endpoint of improved median OS over the placebo arm in patients with CRPC (17.0 vs 15.2 months; HR: 0.89; 95% CI 0.74-1.06).[49] Galeterone is currently undergoing phase II evaluation in patients with CRPC (NCT01709734).[48]

Blocking the androgen receptor

Enzalutamide is a second-generation anti-androgen that binds to the ligand binding domain of androgen receptor with an affinity higher than the first-generation agent bicalutamide. In addition to blocking DHT binding, it impairs androgen receptor nuclear translocation, co-activator recruitment and interaction with DNA.[50] Enzalutamide received FDA approval in 2012 following a clinical trial demonstrating its positive effects on overall survival in the post-chemotherapy setting (18.4 months in the enzalutamide arm versus 13.6 months in the placebo arm; HR 0.63; 95% CI 0.53-0.75).[51] Interim analysis of a more recent clinical trial has now shown that enzalutamide also elicits a small increase in overall survival in the setting of chemotherapy-naïve CRPC (32.4 months in the enzalutamide arm versus 30.2 months in the placebo arm; HR 0.71; 95% CI 0.60 to 0.84).[52] Enzalutamide is relatively well tolerated, with common side-effects including fatigue, diarrhoea and hot flushes. However, seizures occurred in 1% of patients.

Targeting the androgen signalling axis: the future

The therapeutic landscape for prostate cancer has been transformed in recent years, particularly in the context of metastatic CRPC. In addition to abiraterone and enzlalutamide, the last decade has seen approval of chemotherapies (docetaxel and cabazitaxel), the bone-targeted agent denosumab, the immunotherapy sipuleucel-T, and the radiopharmaceutical radium-223. However, these agents have only a modest effect on overall survival, generally in the order of 3-6 months.[45, 46, 51, 53-55]

Two non-mutually exclusive means to improve outcomes for men with advanced prostate cancer are on the horizon. First, better sequencing and/or combinations of the currently approved agents will undoubtedly enhance therapeutic efficacy. Unfortunately, clinical evidence to guide either sequencing or combinatorial therapies is lacking, with treatment decisions being based primarily on predicted toxicity and tolerability. The identification of predictive biomarkers that can enable personalised treatment regimens are urgently required in this context. One emerging example of such a biomarker is the AR-V7 splice variant, which may predict lack of response to abiraterone and enzalutamide.[38] Second, new agents that more effectively inhibit the progression of prostate cancer will likely become available in the near future (figure 1). In terms of agents targeting the androgen signalling axis, new agents of note in clinical development include: the next-generation anti-androgens ARN-509 (which appear to have greater anti-tumour activity, better pharmacological traits and improved patient tolerability than enzalutamide);[56,57] and ODM-201, which has a higher affinity for the androgen receptor than enzalutamide, inhibits androgen receptor nuclear translocation and CRPC growth in preclinical assays, and has shown promise in phase I/II clinical trials;[58] and the aforementioned CYP17 inhibitors (orteronel, galeterone).

Conclusion

The androgen signalling axis drives prostate cancer and is a central target in prostate cancer therapy. The transition period from the initiation of ADT to the onset of CRPC is a crucial time for intervention. While recent advances in targeting androgen receptor signalling in CRPC have improved outcomes, until a cure or more effective drugs against prostate cancer are developed, an estimated 3300 Australian men will continue to die from this disease each year.

Funding

This work was supported by: the US Department of Defense Prostate Cancer Research Program (Transformative Impact Award W81XWH-13-2-0093 to L.A.S., G.V.R. and W.D.T.); the Prostate Cancer Foundation of Australia/Cancer Australia/Movember (Grant IDs 1012337 and 1043482; W.D.T. and L.A.S.); Prostate Cancer Foundation of Australia/Movember Revolutionary Team Award (W.D.T. and L.A.S.); the Ray and Shirl Norman Cancer Research Trust (to L.A.S. and W.D.T.); and a Young Investigator Award from the Prostate Cancer Foundation (L.A.S.). The Adelaide Prostate Cancer Research Centre is supported by an establishment grant from the PCFA (Grant ID 2011/0452; W.D.T., G.V.R. and L.A.S.).

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WHERE DOES CHEMOTHERAPY FIT INTO PROSTATE CANCER TREATMENT?

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Abstract

The treatment of metastatic castrate-resistant prostate cancer has changed dramatically in recent years. Several agents have been shown to improve survival in men with castrate-resistant prostate cancer after docetaxel and, for abiraterone acetate and enzalutamide, in chemotherapy-naïve castrate-resistant prostate cancer patients also. These two drugs are now approved and reimbursed in Australia for use in castrate-resistant prostate cancer after docetaxel, or in men unsuitable to receive chemotherapy. It is reasonable to hypothesise that use of these novel survival-prolonging therapies earlier in the treatment course might improve outcomes and this hypothesis is currently being tested in clinical trials. Cytotoxic chemotherapy is often seen as a less desirable treatment strategy and perhaps some men with castrate-resistant prostate cancer are no longer being considered for this treatment. This perception might also lead to changes in management and prescribing practices, including a shift away from multidisciplinary decision-making. However, a careful review of the available literature suggests that this strategy might not be in the best long-term interests of these men and that cytotoxic chemotherapy, rather than being undesirable, might instead be best used as first line management in men able to receive it.

"No cytotoxic drug or combination has been shown consistently to be useful in prostate cancer."[1] Less youthful readers might recognise that dogma, which was drilled into us as trainees. We learned that prostate cancer did not respond to chemotherapy and this treatment was not worth attempting. We did not understand why and we hoped that one day better drugs or a better understanding of the biology might change things for us. In contrast, today's trainees might consider advanced prostate cancer to be a disease that is amenable to multiple treatment options, and there are more reviews on this topic than primary papers.[2] Now we find ourselves in a very different situation – we have chemotherapy that works, but we also have a relative wealth of other modalities, leading some to question if we should use chemotherapy at all, even though we know it can extend survival and improve quality of life.[3,4]

Our expectations have changed over time. Tannock's 1996 paper showing the palliative benefit of mitoxantrone and prednisone was a turning point for prostate cancer and indeed the broader field of oncology.[5] The combination did not demonstrate significant conventional anticancer activity for what was then called 'hormone-resistant' prostate cancer, now termed castrate-resistant prostate cancer (CRPC).[6] This was to the surprise of no-one at all, but the palliative benefits were both statistically and clinically significant. Chemotherapy for CRPC had finally arrived, although not for the reasons we had hoped, and the delivery of active anticancer treatment for palliation of CRPC was firmly established and became a meaningful trial endpoint.

Effective cytotoxic chemotherapy

Docetaxel was the first cytotoxic agent to challenge the dogma. Two papers published in 2004 established its role, although only the combination of docetaxel and prednisone entered standard clinical practice.[3,4,7] It is worth reiterating the key points of the landmark TAX327 trial. Docetaxel 75mg/m2 every three weeks with prednisone 5mg twice daily, improved survival compared to the previous standard of mitoxantrone and prednisone. The hazard ratio for death was 0.76; if that number sounds familiar, it is because this benefit was comparable to that observed for enzalutamide and for abiraterone acetate (abiraterone) in similar patient populations.[8,9] Median survival was improved with docetaxel from 16.5 months to 18.9 months, but such figures are much less helpful when explaining benefit to patients. Let us not also forget the other benefits of docetaxel treatment: improved pain control (35% vs 22%); improved quality of life taking into account the toxicity of chemotherapy (22% vs 13%); and better probability of PSA response of 50% or more (45% vs 32%).[3] Benefits were perhaps even greater in patients with more favourable PSA levels or kinetics, for those without pain, or those without visceral disease, or older patients.[3,4,10] Ironically, these are the types of patients many multidisciplinary meetings might consider more suitable for non-cytotoxic treatment approaches.

Docetaxel and prednisone quickly became the standard of care for CRPC, although it took several years for

docetaxel to be reimbursed in Australia and even longer in New Zealand. An unintended consequence of the uptake of docetaxel was that it became a defining moment in the course of a CRPC patient: were they 'post-docetaxel' or 'chemo-naïve'? This of course, was a highly arbitrary definition and subject to many variables that are difficult to control, not the least being that there was (and still is) no clear consensus on when and for whom docetaxel should be used. However, the docetaxel treatment status of the patient rapidly became a dividing line for patient management decisions, as well as for clinical trial design and regulatory approval. Patterns of use of docetaxel shifted as newer agents became available only in the post-docetaxel setting and the patterns will no doubt shift again as reimbursed therapies become available for the chemo-naïve patient.

Progress seemed to stop for a while. Satraplatin was supposed to be the next substantial step forward, but although it improved time to progression of disease or pain, it had no benefit for survival and now has sunk without a trace.[11] This did little to instil confidence in cytotoxic drugs, particularly as newer therapies more effectively targeting androgen synthesis and androgen receptor signalling were coming to the fore. Occasional reports have been published indicating benefit for alternative approaches such as metronomic use of cyclophosphamide but these have not entered routine practice.[12] Cabazitaxel was developed on the basis of its activity in taxane-resistant models. The combination of cabazitaxel and prednisone was shown in the post-docetaxel clinical setting to be superior to mitoxantrone and prednisone in terms of survival (TROPIC trial; hazard ratio 0.70; median survival 15.1 months vs 12.7 months), as well as secondary endpoints of response and time to progression.[13] Toxicity was an initial concern, however further experience has shown that toxicity is relatively low and easily manageable. The recommended starting dose of cabazitaxel may be too high and it is bemusing that growth factor support was recommended instead of altering dose and/or schedule, which would be the approach used for palliative treatment of every other solid cancer. The dose issue is currently being addressed in the PROSELICA study (clinicaltrials.gov identifier: NCT01308580) and the role of cabazitaxel in patients who have not received docetaxel is the subject of the FIRSTANA trial (clinicaltrials.gov identifier: NCT01308567).

Optimal timing of chemotherapy

The TAX327 and TROPIC trial outcomes should give us pause, even while we celebrate access to new non-cytotoxic therapies. Docetaxel improves the hazard ratio of death to 0.76. These same patients who then sequence to cabazitaxel experience a hazard ratio of 0.70. We cannot ignore these numbers. Benefits of similar magnitude are seen with abiraterone or enzalutamide when given after docetaxel,[8,9] and similar values are found when those drugs are used before docetaxel.[14,15] However, there is a disturbing thread emerging in the literature to indicate that use of active agents after either abiraterone or enzalutamide might not be associated with the same benefit as initially observed.[16-20] We have made unspoken assumptions that benefits of sequential treatment will be additive, but this assumes that the mechanisms of action and of treatment resistance are independent. This might not be the case. If resistance to androgen receptor-targeted therapies involves mechanisms relevant to the activity of cytotoxic drugs, then the sequence of treatment becomes of critical importance. A similar survival benefit is obtained for both abiraterone and enzalutamide when they are used after docetaxel compared to their use prior to docetaxel. However, the benefit of docetaxel after these agents might be substantially less than the reverse sequence. Given that the median duration of therapy on both agents before chemotherapy is longer than the duration after chemotherapy, for a similar benefit, can it be argued that these agents should be used for the most part only after chemotherapy or if chemotherapy is not appropriate? And where then would cabazitaxel fit into the sequence?

As if that were not enough, we must now consider the implications of the CHAARTED (E3805) clinical trial[21]. CHAARTED brought docetaxel much earlier into the disease sequence, combining it with initiation of androgen deprivation therapy in patients with metastatic castration-naïve prostate cancer. This was controversial, as the regimen combined a cytostatic and cytotoxic approach. The outcomes were extraordinary – six cycles of docetaxel (without prednisone) given with androgen deprivation therapy for metastatic castrate-naïve prostate cancer led to an improvement in the hazard ratio for death of 0.61 for the overall population, with an improvement in median survival from 44.0 to 57.6 months, although the data were relatively immature and were reported after a planned interim analysis after 53% of events. The benefit was clearest for patients with high volume disease (defined as visceral metastases and/or four or more bone metastases with at least one beyond pelvis and vertebral column), where the hazard ratio was 0.6 and median survival improved from 32.2 to 49.2 months. The hazard ratio point estimate for the subset of patients with low volume disease was very similar, but the data are too immature for statistical confidence. Treatment was well tolerated and most patients received the planned number of cycles, 74% without dose modification. Importantly, another similar trial (GETUG-AFU-15) did not show the same outcome and the possible reasons for the discrepancy remain unclear.[22] Nevertheless, the CHAARTED trial is already substantially influencing clinical practice.

Many clinicians adopted this approach as standard therapy, perhaps prematurely, although preliminary data reported at ASCO 2015 from four arms of the STAMPEDE trial (clinicaltrials.gov identifier: NCT00268476) provide additional support for the strategy of combining docetaxel with initiation of androgen deprivation therapy.[23] This analysis assessed survival outcomes for 2692 men receiving standard of care (SOC) androgen deprivation therapy for three or more years, compared to SOC plus docetaxel, SOC plus zoledronic acid, or SOC plus both drugs. Docetaxel was given at a dose of 75 mg/m2 every three weeks for six cycles, with concomitant prednisolone 10mg daily. The analysis included both M1 and M0 castrate-naïve men; 61% had overt metastatic disease. Survival for the whole population was improved for men receiving docetaxel compared to SOC. The hazard ratio for SOC plus docetaxel was 0.76 (95% confidence intervals 0.63-0.91, p = 0.003) and 0.81 (95% confidence

intervals 0.68-0.97, p = 0.020) for SOC plus both drugs compared to SOC. Median survival was 67 months for SOC, compared to 77 months with the addition of docetaxel. No benefit was seen with the use of zoledronic acid.

Sequencing and combinations

The implications of the findings of the CHAARTED and STAMPEDE trials are quite staggering. This is by far the largest effect on survival of any intervention for metastatic prostate cancer since the advent of androgen deprivation therapy. The magnitude of the benefit far exceeds that of docetaxel in the CRPC setting, which implies that the biology of castrate-naïve prostate cancer is fundamentally different in respect of sensitivity to docetaxel and subsequent mechanisms of development of lethal CRPC. Most patients on CHAARTED received treatment in the era when other 'survival-prolonging' therapies were available, as evidenced by the high frequency of use of these agents beyond progression, although not all of the patients in the control arm subsequently received chemotherapy. The findings provide further support for the concept that chemotherapy should be used early rather than late in the disease course. If that is true, then it would be expected that even greater benefits would be seen in the low volume subgroup when data are mature. However, if the principle is true that the treatment might be more effective when used with a lower burden of disease, then one would also predict that even earlier use of docetaxel in the adjuvant setting would provide a similar magnitude of benefit, however this has been shown not to be the case.

CHAARTED also raises several other key points. Firstly, the regimen did not include prednisone and did not assess whether concomitant corticosteroid therapy might further improve outcomes. Inclusion of corticosteroids with docetaxel seemed to enhance the efficacy of treatment in CRPC, but omission of corticosteroids in the CHAARTED population still led to outstanding outcomes. Secondly, the timing of use of docetaxel in this setting is important. It is perhaps not widely appreciated that docetaxel pharmacokinetics are substantially affected by castration status. Clearance of docetaxel in castrate men occurs at approximately double the rate of non-castrate men.[24] The CHAARTED regimen recommends four weeks of androgen deprivation prior to the first cycle of docetaxel. Use of docetaxel earlier than this might be associated with unexpected toxicity.

A third implication of the outcomes of these trials is whether we should now consider all patients treated in this way to be 'post-docetaxel' when planning treatment for subsequent castrate-resistant disease. There is as yet insufficient evidence to support this notion. The different biology of docetaxel in the setting of castrate serum levels of androgens, the complex interaction of docetaxel with androgen receptor biology and modifiers of androgen receptor signalling, and the different clinical outcomes when docetaxel is used in the castrate-resistant versus castrate-naïve settings, all indicate that docetaxel treatment in these two clinical states cannot be considered identical. Until high level clinical trial evidence is available, it remains entirely reasonable to consider docetaxel as a treatment option for these men when their cancer becomes resistant to castration.

Perhaps some clues can be found by looking more carefully at the basic biology and existing clinical data. The mechanism of action of docetaxel remains somewhat unclear, but it has been shown to extend beyond simple stabilisation of microtubules, involving fundamental aspects of androgen receptor biology.[25,26] Preliminary data suggest that the probability of clinical response to docetaxel correlates with sequestration of the androgen receptor in the cytoplasm of circulating tumour cells.[26] Docetaxel treatment of prostate cancers in mice inhibits androgen receptor nuclear localisation and downstream gene expression including PSA, but these effects are not seen if the animals are pretreated with enzalutamide.[27] Humans who receive abiraterone before docetaxel are much less likely to respond to docetaxel.[16,28] Interestingly, in these mice pretreated with enzalutamide, cabazitaxel remains effective,[27] suggesting that this drug might be a more logical cytotoxic option in patients who have already received abiraterone or enzalutamide. Some clinical data now exist to support this idea.[29,30]

Key practice points

Key points for the clinician to understand when choosing and sequencing the available treatment options might include the following:

- Use of abiraterone after enzalutamide assumes that targeting the ligand will be effective after failure of a treatment that effectively blocks receptor activity. This logic may be flawed.
- We know how effective the newer agents are when given after docetaxel, but we have limited information about the activity of docetaxel after the new agents.
- A treatment decision made without appropriate consideration has far-reaching implications. Incorrect choice of the treatment sequence might compromise the ability of the patient to benefit from later treatment options that they will inevitably need. There is little point in changing the sequence of survival-prolonging therapies if by doing so we lose the efficacy of one or more of the agents. We cannot assume that the benefits are additive regardless of sequence.
- These points become even more critical if the pattern of prescribing changes. For example, urologists can easily prescribe abiraterone or enzalutamide, but initial use of docetaxel requires referral to a medical oncologist colleague. The easy option at the beginning might be to the patient's detriment in the end. This highlights the importance of multidisciplinary decision making right from the commencement of therapy and, in the light of CHAARTED and STAMPEDE, perhaps far earlier than we have been accustomed.

What then is the role of chemotherapy for prostate cancer in the current era? We have multiple effective treatment options for CRPC, although none are yet curative. We have no clear evidence to guide us as to the optimal sequence of therapies. We have preclinical and observational data that challenge our underlying assumptions regarding any

cumulative benefit of sequential therapies, as well as the basic biology underlying response and resistance to these therapies. When should a specific therapy start and what should lead us to change treatment? Can we safely and should we combine therapies, such as radium-223 chloride and chemotherapy? There are even more basic questions than these to consider. For example, how many clinicians realise that not all corticosteroids are the same, and that dexamethasone can be a very effective treatment even late in the disease course?[31]

The default answer, and the easy escape for writers of reviews, is to say that more evidence is required and please fund our research. The harsher reality to face is to realise that we all have preconceptions and that we make assumptions all the time based on evidence that might not exist or that we might misunderstand. Chemotherapy was effective in prostate cancer in the 20th century and remains effective in the 21st – if only we knew how to use it correctly.

Conflicts of interest:

IDD is member or chair of advisory boards for the following companies relevant to this paper: Astellas; Bayer; Bristol Myers Squibb; Ipsen; Janssen; Medivation; Sanofi. All payments or honoraria for this work are invoiced by and paid directly to ANZUP Cancer Trials Group, of which IDD is director and chair. No remuneration is received by IDD. CJP has received honoraria and travel support from Sanofi and Janssen.

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EVALUATION OF THE IMPLEMENTATION OF THE PROSTATE CANCER SPECIALIST NURSE ROLE

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Abstract

A national prostate cancer specialist nursing pilot program, supported by Prostate Cancer Foundation of Australia, was launched in May 2012 with funding support from The Movember Foundation. The pilot program aimed to trial a best practice model for providing specialist nursing care to those affected by prostate cancer. Prostate cancer specialist nurses were allocated to 12 hospitals across all Australian states and territories to work in the context of multidisciplinary care. The Prostate Cancer Foundation provided professional development support for nurses through a structured program. This article presents key outcomes from the research commissioned by the Prostate Cancer Foundation to evaluate the prostate cancer specialist nurse role. Specifically, the paper reports evaluation data relating to the roles and functions of the prostate cancer specialist nurse to explore the influence of the role on outcomes for patients, carers and services.

The importance of the nurse's role providing specialist supportive and clinical care is widely recognised in published literature. For many years, the Australian health care system has made provision for specialist nurses for a range of diseases, including breast cancer and chronic illness.[1-4] In response to the potential benefits specialist nursing roles may have for people affected by prostate cancer, Prostate Cancer Foundation of Australia (PCFA) implemented a program to introduce a structured prostate cancer specialist nursing service into Australia.

PCFA launched its prostate cancer specialist nursing program in May 2012. The program involved PCFA working in partnership with health care providers to recruit, train and support a number of prostate cancer specialist nurses (PCSNs) in various locations in metropolitan and regional Australia. The program aimed to trial a best practice model for providing specialist nursing care using a structured format to those affected by prostate cancer, with a view to creating a sustainable model as part of routine cancer care delivery.[5]

The primary objective for the prostate cancer specialist nursing service is to provide direct patient care aimed at improving the patient's cancer experience. The PCSN is an expert point of contact for the man and his family, providing support and care to those affected by prostate cancer. The nurses work alongside other health care providers involved in prostate cancer care and care for men at any point in their cancer journey. They assist men to make optimal use of resources available in their immediate community and streamline service delivery when referral to another centre is required.

PCSNs assist by:

- providing those affected by prostate cancer with an ongoing point of contact and support
- assisting men to access services both in their hospital and in their community during and after treatment
- providing men with reliable information about their diagnosis and treatment plan
- providing men with information about dealing with the effects of treatment and how to get further help to deal with specific problems they may be having
- coordinating care wherever a man is in his cancer journey
- enabling men and families access to support groups
- providing education and training to other health care workers
- participating in projects and service development activities to improve care for those affected by prostate cancer

Health services were selected for the program by PCFA through a competitive application process. Sites were selected from both the public and private sector, assessed against criteria including having a significant prostate cancer incidence rate in the region, providing existing clinical services for men with prostate cancer, and demonstrating engagement of the prostate cancer multidisciplinary team in their application to host a nurse. Rural and regional areas were prioritised to host a PCSN, as were sites with no specialist nursing services or limited supportive care services.

This paper reports selected data from this evaluation to describe the processes involved in implementation of program and the way in which these processes

influenced program outcomes. Additional data reporting the comparison of pre-post program data and other key outcomes will be presented in future publications.

Program evaluation

PCFA commissioned a team led by researchers from Queensland University of Technology to undertake program evaluation. The comprehensive evaluation was undertaken between June 2012 and June 2014, and used a pre-post intervention trial performed within the 12 health services selected for participation in the program. The study protocol was approved by 12 relevant ethics committees at all participating sites and by the university.

This paper reports selected data from surveys, interviews and nurse activity reports to describe the nature and extent of services provided by the PCSNs, and to examine how the roles evolved during the evaluation period. Data from other sources will be reported in future publications.

In addition to completing detailed activity reports, all PCSNs (n=12) were invited to respond to surveys and interviews at the beginning, mid-point and end-point of evaluation. Nurses were informed that their individual responses would remain confidential.

An adapted version of the nurses' work roles and practices, based on the EverCare Nurse Practitioner Role and Activity Scale, was used to assess the extent to which the PCSNs engaged in various role functions in their practice.[6] Additional questions were added to assess beliefs and expectations regarding the role, and perceptions of its effectiveness. The PCSN activity reports were recorded on a daily basis to document clinical and strategic activity undertaken by the nurses throughout the data collection period. These reports were recorded on iPad and submitted on a monthly basis.

Outcome from evaluation

Role related activities

To understand the role of the PCSN, data were collected on the frequency with which the nurses undertook a range of activities relevant to their roles. A summary of the frequency with which various roles were implemented in presented in table 1.

***Table 1**: Prostate cancer specialist nurses' self-reporting of role related activities.*

Domain	**Role-related activities performed daily**
Direct nursing care	Read and consider results from diagnostic tests performed. Conduct a psychosocial assessment.
Team communications	Document and manage clinical caseload activity data relevant to the role.
Domain	**Role-related activities performed weekly**
Direct nursing care	Educate men and/or families about the appropriate health care professional to contact if issues/concerns arise.
Clinical care management	Discuss queries or health status changes with patient and family and support them as they deal with changes. Monitor and follow up men with ongoing complex needs.
Patient education in the clinical context	Educate patient and family about the disease state and/or progression.
Care management plan	Collaborate with patient to ensure care management plan is patient-focused and incorporates individual needs.
Patient advocacy in the clinical context	Provide men and families with strategies to ask questions or raise issues during consultation with a health care professional.
Multidisciplinary clinical care	Provide input to the care management team who provide care. Communicate with senior nursing staff regarding patient's treatment or care. Participate in multidisciplinary team meetings. Communicate with multidisciplinary team regarding patient health status changes and care issues.

Domain	Role-related activities performed monthly
Education services	Educate nursing staff to enhance their ability to recognise changes in men's conditions. Educate nursing staff about care management plan and planning.
Strategic tasks	Collaborate or conduct strategic meeting/s with one or more PCSNs. Communicate/meet with various organisations to establish PCSN service provision/referral process.
Team Communications	Provide informal/formal mentoring or orientation to other nurses.
Domain	**Role-related activities performed yearly**
Strategic tasks	Undertake audit/quality improvement projects. Contribute to, or, provide feedback for health system strategic, developments/reforms/proposals. Attend health related professional development course/conference/symposium relevant to my role.

***Table 2**: Proportion of time spent on specific activities by the prostate cancer specialist nurses.*

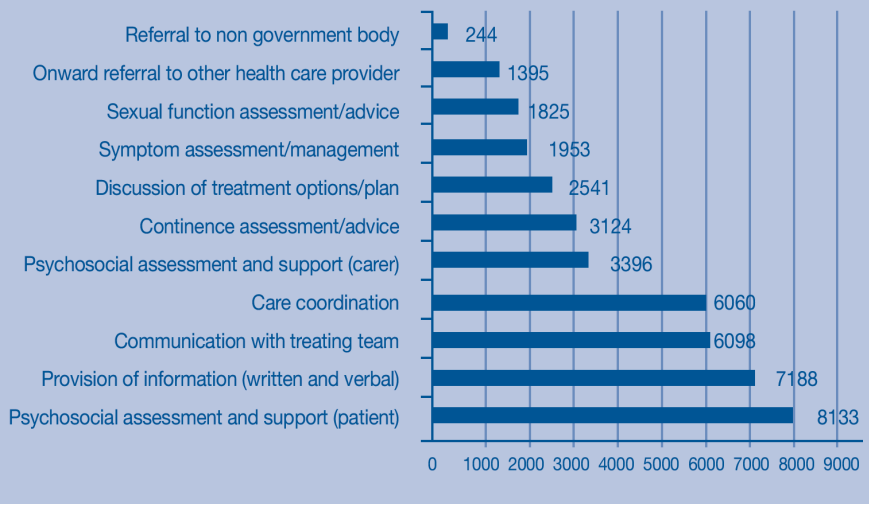
Paid working activities	Proportion of time (%)		
	Beginning of evaluation	Mid-point of evaluation	End-point of evaluation
Clinical consultations	56.8	46.1	52.5
Strategic/non-clinical activities	16.8	25.7	25.8
Administrative activities	26.4	28.2	21.7

Table 2 shows the proportion of time spent on each of the work-related activities by the PCSN. The nurses spent around 50% of time on clinical consultation at each point in the evaluation period. Compared to the beginning of the evaluation, PCSNs spent less time on administrative activities and clinical consultations, but more time on strategic and non-clinical activities at the end of the evaluation.

These data confirm the broad role functions of the PCSN across various clinical and strategic activities. As the PCSNs developed their practice, their involvement in more strategic activities increased. This highlighted the important role PCSNs play in achieving broader system level and local service improvements.

During the reporting period, PCSNs made patient-related contacts and provided a range of nursing services. The types of intervention are shown in further detail below in figure 1.

***Figure 1**: Types of intervention delivered by the PCSNs during the evaluation period.*



Across all sites, the most frequently delivered interventions were psychosocial assessments and support for men (75%), followed by provision of information (68%), communication with treating teams (57%) and care coordination (56%). Rural men were more likely to receive the following interventions than those not living in a rural area: psychosocial assessment and support to carer; provision of information; continence and sexual function assessment/advice. However, rural men were less likely than men in metropolitan settings to receive interventions related to psychosocial assessment and support for the patient, and communication with the treating team.

The following exemplars demonstrate the role function as seen as useful by users of the service:

- "The answering of questions not able to be raised with the doctor."
- "Providing an important link between different health services."
- "Providing information on what was going to exactly happen with the surgery and information on side-effect management."

These data confirm the importance of the role that PCSNs play in psychosocial care and information provision. Differences between rural and metropolitan areas emphasise the need for flexibility in service provision to ensure population needs are addressed.

Patient-related contacts

Overall, around 21% of contacts were with men who were newly diagnosed or within one month of diagnosis with prostate cancer, 37% were with men diagnosed for one to six months and 30% with those diagnosed for more than one year. There were differences between sites in terms of length of time since diagnosis when PCSNs made patient-related contacts. This pattern also shifted over time. During the second half of the reporting period, more contacts were made with men who had been diagnosed for a longer duration. Men from a rural area were more likely than those in a non-rural area to receive the PCSN service when they were newly diagnosed or diagnosed for six months to two years.

The PCSN provided consultations by men affected by prostate cancer for various reasons. Across all contacts, the most common reason for PCSN contact was: planned review assessments (35%); conducting new patient assessments (23%); and patient initiated contacts (22%). There was variation across sites in the primary reasons for patient contact.

Across all sites, most interventions (63%) were delivered in less than 30 minutes and very few were delivered in longer than two hours. However, there was variation between sites. Over the reporting period, nearly all sites showed statistically significant changes in the length of intervention performed by the PCSN. The length of intervention per episode was longer during the second half of the reporting period than in the first half. This change may be due to a greater focus on provision of services to men with more complex needs as the nurse developed his/her skills.

The length of intervention was significantly different by whether or not contacts were made with men from a rural area. Men from a rural area were more likely to receive interventions longer than 30 minutes per episode than those not from a rural area.

These data highlight that the service reached men across all stages of their cancer journey, and that over time, nurses were more likely to reach men earlier in their disease trajectory. Differences between rural and metropolitan settings indicate that access issues can be addressed by using flexible approaches to service delivery.

During the reporting period, the outcome of the majority of patient-related contacts was follow-up appointments (78%). About 22% of all contacts were discharged with open referral. Other outcomes of patient-related contacts include admitting men to hospital, following up with telephone reviews, or men no longer needing or wanting any intervention.

The PCSNs perceived their level of influence on key outcomes to be greatest in the following areas:

- Every patient is aware of their pathway of care (66.7%).
- The patient is satisfied with their cancer care (66.7%).
- The family/carer is satisfied with their cancer care (75%).
- There is an effective multidisciplinary team relevant for each cancer (66.7%).
- Men's knowledge of and access to services, especially primary care, is improved (83.3%).
- Men receive adequate information to make treatment decisions (75%).
- Men receive appropriate supportive care (83.3%).

Consistent with the expected aims of the program, these data demonstrate that nurses perceived their role had impacted on many key outcomes for men and their carers.

Conclusion

Program evaluation has demonstrated the PCSN played an important role in providing key services to meet the needs of men with prostate cancer. These services

are integral to improving the cancer pathway of those affected by prostate cancer across different stages of the disease. The findings also indicate that PCSNs became well integrated into the multidisciplinary team within their service over time.

PCSNs have broad role functions including engagement in a range of clinical and strategic activities. Differences between rural and metropolitan areas emphasise the need for flexibility in service provision to ensure population needs are addressed. As the nurses developed their practice, their involvement in more strategic activities increased, suggesting that establishment of PCSNs services are likely to play an important role in achieving broader system level and local service improvements.

Consistent with the expected aims of the program, PCSNs perceived their role impacted on many key outcomes for men and their carers. The benefits of using a structured model to ensure consistency in care delivery and to ensure a nationally collaborative approach is likely to be critical to the success of such programs.

Implications for practice

A number of recommendations emerge from the evaluation that have the potential to improve the services for those affected by prostate cancer. Specifically, the data indicate that having a defined service model enabled the prostate cancer specialist nursing service to facilitate a common practice model that was implemented with a degree of flexibility to ensure the service met the needs of the local prostate cancer population. Such models are important to guide service providers to ensure appropriate standards of care are delivered, and unexplained variation in practice is reduced. The findings also suggest great potential for the PCSN role. Consideration should therefore be given to ways to optimise the scope of the PCSN's practice through new models of practice including nurse led clinics. Moreover, given the broad range of functions that PCSNs have within the context of multidisciplinary care, it is important that emphasis be placed on expert nursing consultation functions, with administrative functions being limited to enabling that function only. As more men and families become aware of the role of the PCSN and request access to this service, strategies need to be implemented to ensure growth and sustainability of the service through appropriate funding models.

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ADVANCING PROSTATE CANCER SURVIVORSHIP RESEARCH IN AUSTRALIA

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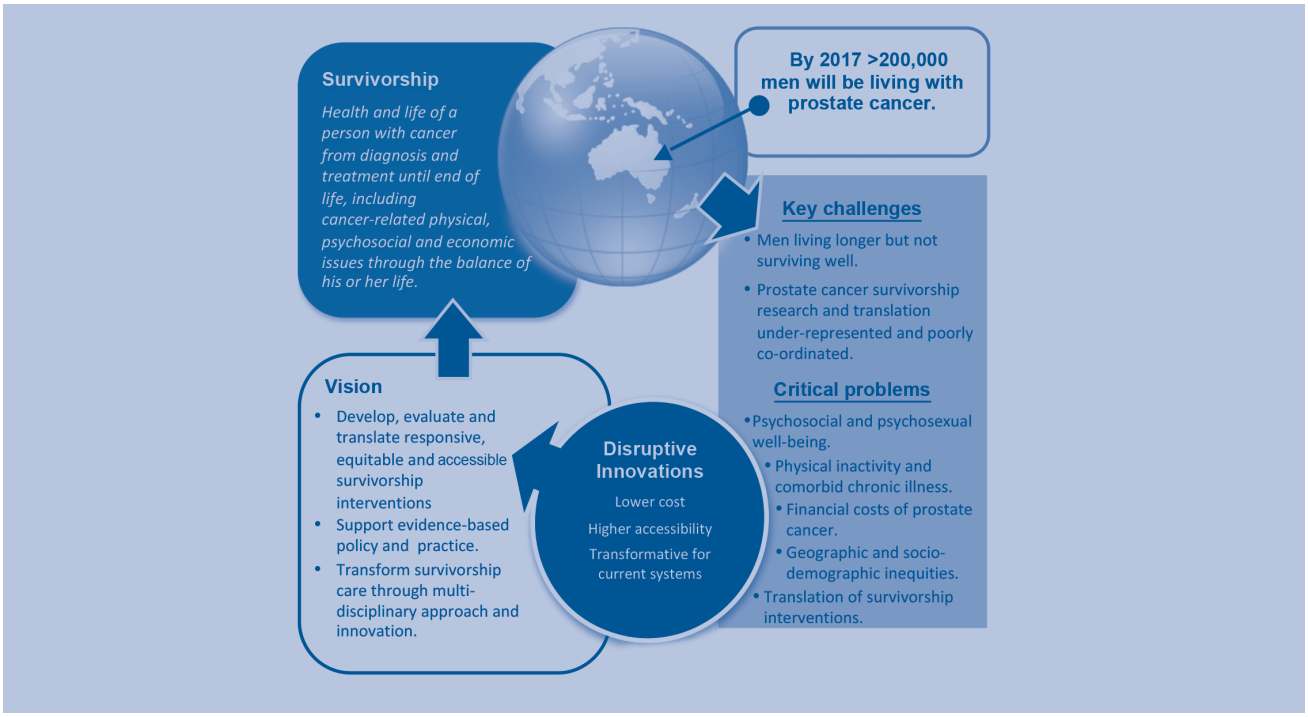
Abstract

Prostate cancer is the most common cancer affecting Australian men, with 1 in 7 males diagnosed before the age of 75 years and most now surviving long-term in the absence of adequate and accessible supportive care for their wellbeing. A substantive proportion of men with prostate cancer experience heightened psychological distress and ongoing unmet needs for supportive care in the domains of sexuality and psychosocial care. This perspective focuses on: men's psychosocial and psychosexual needs; the role of exercise in survivorship care; health economics; and geographic and sociodemographic disparities in outcomes. It is proposed that prostate cancer survivorship research, translation and education needs to articulate with key factors that influence the acceptability and uptake of services. Stepped care approaches are also needed to meet the challenges of increasing prostate cancer prevalence taking into account constraints in health care resources and unique barriers to care such as geographic location, health literacy, and other aspects of social disadvantage. Finally, close linkage to to community with the patient and family placed at the centre of the care model will be crucial.

Prostate cancer is the most common cancer affecting Australian men (excluding keratinocyte cancers), with 1 in 7 males diagnosed before the age of 75 years. The scale of the challenge is immense – five-year relative survival rates for prostate cancer in Australia have increased dramatically from 58% in 1982-87 to 92% in 2006-2010.[1] In 2008 and 2009, prostate cancer was the highest ranked male cancer in terms of health system expenditure in Australia, totalling $347 million or 14% of the total male health system expenditure on cancer.[2] By 2017, there will be more than 200,000 men living with prostate cancer in Australia and 80% of these men will be long-term survivors.[3,4]

Although many more men are surviving prostate cancer than ever before, they are not necessarily surviving well.[6] Survivorship encompasses the health and life of a person with cancer from diagnosis and treatment until end of life, including cancer-related physical, psychosocial and economic issues through the balance of his or her life, and within this the experience of his or her family, partners and caregivers.[6] Men are now

***Figure 1**: Prostate cancer survivorship*



living longer with ongoing physical, psychosexual and practical burdens related to diagnosis and treatment of their prostate cancer, with these effects compounded by high rates of comorbid illness that relate to lifestyle factors such as inactivity and obesity.[8] Problematically, evidence demonstrates that men's supportive care, physical, practical and informational, emotional and psychological needs are not being met in any systematic way.[9] There are several challenges and barriers to obtaining the best possible survivorship outcomes for men with prostate cancer, and large gaps in knowledge that urgently need to be addressed. This perspective focuses on: psychosocial and psychosexual needs; the role of exercise in survivorship care; economics of new and existing interventions; and geographic and sociodemographic disparities in outcomes. A model proposing a way forward is presented (see figure 1).

Psychosocial and psychosexual care

In Australia, between 10 and 23% of men diagnosed with prostate cancer report high levels of psychological distress.[7] Other studies have found a 17.5% prevalence of depression in men with localised prostate cancer,[8] and an eight-year longitudinal study found that 30–40% of men reported ongoing health-related distress, worry, feeling low and insomnia.[9] Men's risk of suicide is increased in the first six to 12 months after the diagnosis of prostate cancer,[10-12] and recent research has found that men with prostate cancer have an increased prevalence of suicide relative to population norms, with risk increasing with time from diagnosis.[7] Early high distress is a predictor of ongoing high distress and hence detecting heightened distress early is a key priority.[9-13] However, men are typically low users of psychological support services for cancer and are less likely than women to discuss their psychosocial concerns with their health care providers.[14] This means their distress is often unnoticed and untreated. Effective (and cost effective) approaches to psychosocial care for these men will likely require screening for distress and tailored problem assessment to efficiently direct psychosocial care services to where they are needed most,[15] including a mechanism for stepping up the intensity of care when problems do not resolve.[16]

Sexual dysfunction is arguably the most highly prevalent long-term deleterious side-effect of prostate cancer treatment. Current treatments commonly result in erectile dysfunction, often accompanied by loss of desire and difficulty reaching orgasm.[17] All active treatments for prostate cancer have been found to be associated with long-term poorer sexual outcomes, with prevalence rates for erectile dysfunction ranging from 36% to 87%.[18,19] The mainstay of treatment for erectile dysfunction is medical management that if administered early in the course of recovery, may assist with smooth muscle preservation and improve erectile function through increased tissue oxygenation.[20,21] However, many men are reluctant to seek medical help for erectile dysfunction even when bothered by their poor erections, with satisfaction and adherence to treatments often poor.[17,22] Unmet sexuality needs are highly prevalent in these men.[23,24]

To date, interventions to address intimacy and sexual outcomes for men with prostate cancer have reported low recruitment (22%), high attrition (up to 50%), small sample sizes and equivocal or disappointing results.[25-29] Our group has undertaken the largest randomised trial to date delivering psychosexual support to couples after surgery for prostate cancer. While men in the two intervention arms used medical treatment for erectile dysfunction more frequently than men in usual care, no significant effects were found for sexual function, unmet sexuality needs, or sexual self-confidence. This study provides further evidence that current best practice approaches to psychosexual treatments for prostate cancer, based largely on expert opinion, may not translate into better sexual outcomes.[30] Theory building foundational research is needed in this area that applies masculinity and life course models and relevant behavioural frameworks to better understand men's response to prostate cancer related sexual dysfunction.[31,32] From this, a theory-based and improved model of psychosexual intervention could then be developed, tested and, if effective, translated into practice.

Integrating exercise medicine into survivorship care

Research has consistently demonstrated that exercise improves physical and mental health in men with prostate cancer during and following completion of targeted exercise interventions.[33-39] More specifically, resistance and aerobic exercise have been shown to enhance the musculoskeletal system, improve cardiorespiratory capacity and prevent functional decline, as well as improve sexual health and overall quality of life in men with localised prostate cancer.[37,40-42] Few studies have examined the impact of exercise in men with advanced bone metastatic disease.[43] In the setting of active surveillance, preliminary studies involving basic exercise advice report decreased numbers of patients undergoing prostate cancer active treatment, as well as modulation of the biological processes involved in tumorigenesis.[44,45] Kenfield and colleagues demonstrated a 61% lowering risk of prostate cancer death in men who regularly engage in vigorous physical activity.[46] These findings have been recently confirmed in a large cohort study of 4623 men diagnosed with prostate cancer, where prostate-specific mortality was significantly lower in men walking/cycling 20 minutes or more/day or exercising for at least one hour/week,[47] adding to the growing body of evidence suggesting that exercise may extend survival for cancer patients.[48,49] Exercise may suppress tumour progression with a range of mechanisms proposed including improved immune function, reduced systemic inflammation, epigenetic modulation, beneficial myokine and adipokine profiles,[50] telomere alterations,[51] as well as exercise effects on endocrine function including the insulin/IGF axis.[52] Maintaining or increasing muscle mass, as well as regular high intensity activation of these tissues, has potential to produce endogenous medicine, which suppresses tumour progression as well as reducing metabolic and cardiovascular disease.[53]

Novel approaches to ameliorating treatment toxicities of 'super-castrate' androgen deprivation therapy (ADT), as well as chemotherapy in prostate cancer, are also urgently needed. ADT has proven highly successful in slowing or even reversing the progression of certain prostate cancers and is a much used pharmaceutical approach in the management of men with both localised and metastatic disease. However, for some patients, prostate specific antigen (PSA) serum levels or PSA velocity starts to increase, indicating the cancer is proliferating and is now termed castrate resistant prostate cancer (CRPC).[54] There are several new drugs (e.g. abiraterone and enzalutamide) now available in Australia which are being prescribed for CRPC patients, however patients may experience treatment toxicities. In 2013, the team at The Institute of Cancer Research who developed abiraterone acetate, published a paper reporting the changes in body composition accompanying maximal androgen suppression with abiraterone acetate in men with CRPC.[55] Significant and clinically meaningful alterations in muscle and fat composition resulted from abiraterone acetate, with between 2.8 and 4.3% decline in muscle over a median of 7.5 months. This study highlights concerns about development of significant sarcopenia and increased visceral fat in patients on abiraterone acetate, which is in addition to the previously reported toxicities of this drug. Low muscle mass and high body fat termed 'sarcopenic obesity', is a particularly high risk condition for a range of chronic diseases, in particular metabolic syndrome, type II diabetes and cardiovascular disease. It is also a perfect storm driving functional decline, increased risk of falls and fractures, and ultimately lower quality of life and even death, although not directly attributable to the cancer. In addition, chemohormonal therapy (ADT + docetaxel) is being trialled over ADT alone in men with high volume newly metastatic prostate cancer.[56] These two developments are rapidly resulting in considerably changed practice in the management of men with advanced prostate cancer, including metastatic and CRPC. While exercise medicine has the potential to significantly ameliorate treatment toxicities of 'super-castrate' ADT treatments as well as chemotherapy, no study to date has been conducted to empirically evaluate this, or even if such an intervention is safe and feasible.

Economic costs of prostate cancer

Healthcare costs are rapidly growing in Australia and driven by new technologies in the form of more expensive services and therapies, more services per patient, and an increasing population that is ageing.[57] Healthcare expenditure for prostate cancer is no exception and this means, compared with a decade ago, men diagnosed and treated with prostate cancer

today receive more tests, services and treatment combinations than ever before.[57] It is expected that this increased spending translates to better life expectancy, but also better quality of life for these men. Few studies have measured healthcare costs for men with prostate cancer - the best known in Australia is Gordon et al,[58] which measured Medicare Benefits Scheme/ Pharmaceutical Benefits Scheme and out-of-pocket costs only; hospital inpatient and outpatient costs were not reported. It is important to understand the full range of financial implications of existing and new treatments for prostate cancer. Currently, although several studies have estimated a limited proportion of costs,[59-61] the full costs to the health system, costs to the individual and to society are not fully understood.

Frequencies of use and costs of different treatments vary substantially across Australia and by age at diagnosis.[58] For example, the average cost to the Medicare Benefits Scheme and Pharmaceutical Benefits Scheme per man treated with ADT was $18,622 in 2011; radical prostatectomy was $7810 and external beam radiotherapy $14,307.58 Hospital costs of outpatient care, diagnostics and out-of-pocket expenses are additional costs. Moreover, the effects on recovery time, quality of life and survival vary by treatment modality. Identifying the interventions for different stages of disease that provide the best patient outcomes and are considered to be good value for money is fundamental. In order for Australia to have an efficient and more sustainable healthcare system, new technologies need to be assessed for their cost-effectiveness. Cost-effectiveness is the process by which the health expenditure required to implement an intervention is judged against the value of health and health gain it can produce, relative to the next best alternatives. Choices that are made by decision makers to eliminate products and services that are not cost-effective, free resources for existing healthcare provision and for new services. It is therefore crucial that emerging technologies and supportive care interventions for prostate cancer are based on sound cost-effectiveness to provide the best healthcare outcomes for Australian men. Emerging technologies for prostate cancer include several focal therapies, proton beam radiation, multi-parametric magnetic resonance imaging for diagnosis, robot-assisted surgery, and new drug therapies for advanced prostate cancer, among others.

Geographic and socio-demographic inequalities

Critical geographic and socio-demographic differences in mortality rates and survival outcomes for men with prostate cancer are not well described or understood.[62] Our recent systematic review found strong evidence that, both in Australia and internationally, prostate cancer outcomes are associated with where men live and their ability to pay for health care.[63] Men living in urban or affluent areas had higher rates of PSA testing, higher prostate cancer incidence, lower risk of advanced prostate cancer, better survival, greater access or use of medical services and lower mortality rates than men living in rural or disadvantaged areas respectively. If anything, despite increasing stakeholder and media attention, and the implementation of health policies and programs designed to reduce the urban-rural inequality,[64] these inequalities have increased over time.[62,65-68] Moreover, the magnitude of the urban-rural inequality is increasing over time.[62,65-68] In Australia, men diagnosed with prostate cancer while living outside the capital cities, were 24% more likely to die within five years of diagnosis,[62] with two studies in NSW showing that this poorer survival for men living in rural and remote areas remained after adjustment for stage at diagnosis.[68,69] Given the high prevalence of prostate cancer in Australia, these disparities are a cause for national concern.

We urgently need an understanding of why survival and other outcomes for Australian men diagnosed with prostate cancer depend on where they live. Unless we better understand the reasons for observed inequities, and the important issues faced by prostate cancer patients in rural, remote and disadvantaged areas, these inequities will remain and men will continue to have poorer outcomes as a result of where they live. To date, there have been no systematic investigations of small area patterns of prostate cancer incidence and survival at a national level, limiting the ability to obtain sufficient information to appropriately intervene. We propose two ways forward here, first to undertake complex spatial modelling and visualisation methods to quantify the extent of small area geographical differences in prostate cancer outcomes. Second, to apply a mix of ecological analyses on the small area estimates, combined with qualitative studies to identify those risk-modifying factors that are associated with prostate cancer outcomes, and how these factors vary by geographical area.

Prostate cancer survivorship research and practice

Increased survivor numbers and disparities among those affected challenges society, the healthcare system and its workforce. However, survivorship research in prostate cancer is underrepresented nationally and internationally compared to basic and clinical research in prostate cancer, and relative to breast cancer survivorship research; in Australia and elsewhere the effort is poorly coordinated across disciplines and jurisdictions.[7-72] In an international scan of research and translation in prostate cancer survivorship, we concluded that there was currently no clearly evident systematic national or international approach to the transfer and dissemination of knowledge and skills for enhancing prostate cancer survivorship, a conclusion also supported by published comment in the recently released American Cancer Society survivorship guidelines.[73] In Australia and

elsewhere, evidence-based survivorship care for men with prostate cancer is the exception rather than the rule. The problem is exacerbated by already high and dramatically increasing prostate cancer prevalence – an ensuing high health care services load for these patients – and centralisation of specialist services resulting in geographic and socioeconomic barriers to access. Current research and practice in prostate cancer survivorship in Australia is disjointed and disconnected across community and acute settings, disciplines and state boundaries.

Conclusion

In order to produce real outcomes for men and their families, prostate cancer survivorship research, translation and education needs to: articulate key factors that influence the acceptability and uptake of services;[31,32] apply stepped care approaches to meet the challenges of increasing prostate cancer prevalence, constraints in health care resources and unique barriers to care such as geographic location, health literacy and other aspects of social disadvantage;[74,75] link closely to community;[76] and place the patient and family at the centre of the care model.[77] We believe this approach, linkage and collaboration between all key groups is critical to make a meaningful difference in the lives of men with prostate cancer, not only in Australia but globally.

Acknowledgements

We would like to thank Mark Frydenberg, Helen Crowe, Melissa K Hyde, Kevin D Stein, Lisa G Horvath and David M Roder for their support of this research perspective.

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CANCER CONSUMER INVOLVEMENT IN RESEARCH IN AUSTRALIA

Sally Crossing AM
21 July 2015
Chair, Cancer Voices NSW

Celebrating 10 years (2005 – 2015) of Cancer Voices' consumer involvement in research program

Cancer Voices is the independent volunteer voice of people affected by cancer in NSW. Following is a brief overview from first advocacy steps towards what is now a well-developed program of consumer involvement and engagement in cancer research.

Why is consumer involvement in research important?

The first years of this century saw substantial evidence and acceptance of the need to make research efforts more effective and relevant by engaging stakeholders – consumers, clinicians and funders (government and charity), in selecting research questions, designing studies and making funding decisions. The central challenge has been to engage meaningfully with consumers.

Also studied and accepted has been the acknowledgement that consumer involvement can and does add value to research. Most funders now realise that their donors are more engaged when they can be assured that research funded by their charity or institution is not only of high scientific merit, but also includes the needs and views of those who will ultimately benefit by it - consumers. A number of funders now require evidence in grant proposals that effective consumer engagement has indeed taken place.

Cancer Voices quickly recognised these issues and that it was well-placed to provide an informed consumer view, either as a group, or through its nomination of informed, broad-view consumers. This allows Cancer Voices to concentrate on research which could improve cancer diagnosis, treatment, care and survivorship – core aims for Cancer Voices.

History

Cancer Voices was founded in NSW in October 2000, by a group of cancer consumer advocates who recognised the need for a combined voice about issues of interest or concern for people affected by cancer. As a volunteer, unfunded consumer organisation, we realised that to implement our recommendations and policy we would need a strong, committed, well-resourced partner. For our consumer involvement in research purpose, the perfect partner was Cancer Council NSW, the state's preeminent cancer charity and funder of cancer research.

Being aware of early positive developments overseas, especially in the US, Cancer Voices put a three pronged proposal for consumer involvement in research, through its representative on the Cancer Council's Cancer Research Committee in November 2001, and to its Board in December 2002. These were:

i. Increasing the rate and level of consumer involvement in the development of cancer research projects.

ii. Collecting and promoting consumers' priorities for cancer research.

iii. Ensuring consumer participation in cancer research funding decisions and review.

Cancer Voices began to work closely with Cancer Council NSW staff towards implementing these goals, supported by peer reviewed studies, over 2002-2004.[1-3]

Implementation

Training for consumers

Cancer Council NSW and Cancer Voices agreed that for involvement to be meaningful and useful to researchers and funders, potential 'engagees' needed to have an interest in research and the opportunity to understand its five main streams, the research process and cycle, governance and ethics, as well as opportunities for consumer involvement. We worked together to develop a short training course, to be offered annually at least.

In 2005, the first formal training for consumers interested in involvement was held so that consumers could:

- assist Cancer Council NSW in review of grant proposals each year through a Consumer Review Panel.
- be introduced to the world of cancer research so as to be able to provide the informed consumer view to specific cancer research projects. This became important as cancer research funders required evidence that this had occurred, and as a funding criteria.

Consumer priorities for cancer research

After surveying its members about directions of research over some years, Cancer Voices proposed that a wider Consumer Research Forum be held. This took place, again in partnership with Cancer Council NSW, on 14 May 2009, with a reach beyond Cancer Voices members from

around Australia. We used the 'global café' technique so that all 40 participants could discuss and log their priorities on five major cancer research topic areas. The outcome of this exercise has been used by Cancer Voices to alert researchers and funders to consumer priorities. We subsequently published a peer reviewed paper to inform other interested cancer research funders about what people affected by cancer would like to see researched.[4]

Linking researchers with informed consumer advisors

Cancer Voices' consumer involvement in research matching program is probably its most innovative product and service. The process is facilitated by an online application form in which researchers are asked to provide all the information needed for Cancer Voices to 'match' them with an informed consumer advisor for their project – preferably as early in the cycle as possible. Consumers are sourced from Cancer Voices' database of people who have attended training. After expressing interest, their nomination is provided to the requester. Both researchers and nominated consumers receive a Cancer Voices Guide which clarifies their respective roles and expectations (www.cancervoices.org.au).

Priorities directly initiated and funded – two examples

Cancer Voices consumer representatives proposed the concepts and participated in the design, development and implementation of two projects which reflected identified consumer priorities:

- Australian Cancer Trials Online project with University of Sydney, Australia and New Zealand Clinical Trials Registry and Cancer Australia, which received a National Health and Medical Research Council grant. The ongoing outcome of this research is a consumer friendly website (www.australiancancertrials.gov.au) which facilitates searches for suitable clinical trials – a gap identified by consumers and with high potential to increase participation in clinical trials.[7,8] This concept was later taken on by the National Health and Medical Research Council and applied to all clinical trials.

- Pharmacogenomic Research for Personalised Medicine – another Cancer Voices initiative, taken up by a consortium of seven institutions and funded for five years by Cancer Council NSW. Our aim was to speed up progress in his area of research by encouraging collaboration between the best researchers in the state. A very successful collaboration, which continues post funding.

Consumer review

Cancer Council NSW again led the way in establishing Australia's first fully fledged Consumer Review Panel. Using defined criteria to rate grant applications, consumers consider up to 30 each year. Originally their rating was weighted at 20%, with standard scientific merit review via peer review assessment at 80%. This was soon (2007) upgraded to 50-50%, a clear commitment to the value of the consumer process.

Other government agencies, cancer charities and research institutions have adopted the main elements of the Consumer Review Panel role, to greater and lesser degrees. Most also incorporate training using methods and material originally developed between Cancer Voices and Cancer Council NSW. Early adopters include Cancer Australia, the National Breast Cancer Foundation, Kolling Medical Research Institute, Macquarie University Medical Research Institute, Lowy Cancer Research Centre and the Kinghorn/Garvan Research Institutes.

Significance and future

Cancer Voices sees value in sharing this successful model. Four peer reviewed journal papers have been published about the program (see below) and are frequently cited. Cancer Voices and Cancer Council NSW have made presentations to, and had posters accepted by a number of Australian cancer conferences over the 10 years since implementation fully began. This is an excellent example of consumers, the people affected by cancer, partnering with an organisation which could make their proposals really happen. More importantly it has shown that the involvement of consumers in research does make a valuable difference, and has become well accepted by funders and researchers alike.

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CANCER COUNCIL AUSTRALIA STUDENT ESSAY COMPETITION

RESEARCH AND THE CHANGING LANDSCAPE OF ONCOLOGY: THE JOURNEY OF CANCER CONTROL

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Cancer, though defined simply as the uncontrolled growth and spread of cells,[1] is one of today's most complex and significant global health burdens, accounting for approximately 1 in 7 deaths worldwide. This accessibility has fuelled a powerful and effective drive for research into cancer control over a long period of time, and hence an ever-transforming landscape of oncology. Research has been the single greatest catalyst for positive change within oncology, manipulating the field as it empowers us with greater understanding and more effective methods of cancer control.

This essay will explore how research has served to change the landscape of oncology over time - from where we have come, to where we presently stand. It will discuss important contributions from research along the way that have effected change and served to significantly shape the field in the domains of prevention, screening and detection, as well as treatment - and also examine the future direction of cancer control. Finally, the significance of this to students of medicine as they prepare to work with and for patients in this dynamic field will be considered.

Laying the foundations of oncology

"You cannot move forward in changing the landscape of cancer without knowing what that landscape was and is and how it can be influenced in the future."

- Siddhartha Mukherjee, MD, PhD

Recognition of the process of cancer dates as far back as 2500BC in Egypt, when a report on removal of 'tumours of the breast' was written.[2] It stated the tumour was cauterised, with the note: "There is no treatment."[3]

Research, in the form of autopsies, began to broaden the landscape of oncology from the 16th century. It was precisely this task that saw the birth of research into cancer, a dismissal of spiritual or religious aetiology and a drive to prove or disprove theories through science. Autopsies had a dramatic effect on our understanding of the human body, with the discovery of the lymphatic system and the hypothesis that abnormalities within it were the primary neoplastic cause.

The advent of anaesthesia in 1846 expanded the scope of surgery, and research into cancer flourished alongside it. Treatment of cancer advanced, with development of procedures such as the radical mastectomy.[4]

This, combined with the use of the modern microscope, allowed the correlation of disease with micropathology. Research through this format was able to identify cancerous cells, as well as the concept of metastasis. Treatment thus changed, with surgeons Bilroth, Handley and Halsted pioneering operations that included removal of the primary tumour in conjunction with regional lymph nodes.[5] The landscape of oncology evolved indelibly.

Through surgery and the pathologic study of cancer, research up until this point in time provided firm foundations for modern day oncology.

Modern day landscape

Genetic basis of cancer

In 1953, the chemical structure of deoxyribonucleic acid (DNA) was deduced by Watson and Crick.[6] Knowledge of the human genome (which was to be extended some years later by the Human Genome Project) enabled researchers to soon develop an understanding that cancer was caused by mutations in genes, either inherited or spontaneous. This was a turning point in cancer research, sparking a novel era of genetic research, with a focus on nucleic acids, receptors and signal pathways.

Two important discoveries that followed on from here were that of oncogenes – genes that drive uncontrolled proliferation of abnormal cells – by Bishop and Varmus,[7] and tumour suppressor genes – genes that work to oppose proliferation of aberrant cells,[8] by Knudson.[9] From here, scientists were able to identify specific genetic changes that could lead to cancer, which had groundbreaking implications for clinical oncology in areas of prevention, detection and treatment, moulding its landscape in a revolutionary manner.

Prevention and screening

An 'early detection and treatment' philosophy dominated until the 1960s, with renewed research into carcinogens. By 2014, the World Health Organisation had identified over 100 chemical, physical and biological carcinogens. Phenomenal reductions in cancer incidence and mortality have occurred through our knowledge of these, and today one third of cancers are preventable.[10]

The impact of preventative research is best evidenced by the transformation of our approach to cervical cancer. Micropathological research led to the development of the Pap test in 1928.[11] This simple screening test allowed abnormal cervical cells to be identified and removed, prior to cancerous transformation. Australian cervical cancer incidence and mortality has halved since introducing its screening program in 1991.[12]

Compounding this research was the later discovery that persistent infection with high-risk strains of human papillomavirus (HPV) was responsible for the vast majority of cervical cancers worldwide, having huge implications for cervical cancer control.[13]

It was Australian research that led to the development of a cervical cancer vaccine, Gardasil, which protects against high-risk HPV types 16 and 18.[14] It has largely been tested as successful, with an almost 100% rate of preventing cervical cancer.[15] Thus, Australia implemented a school-based National HPV program in 2007, which is forecast to cause significant reductions in cervical cancer incidence and mortality, with studies already highlighting reductions in cervical abnormalities.[16]

It is now understood that virus-related cancers represent approximately 15% of total cancer incidence globally,[17] and continued research into this area of prevention hence holds great potential.

Detection

Breast cancer in particular has benefited from research into innovative and improved detection methods. Detecting breast cancer early and while it is relatively smaller, is strongly associated with increased treatment options and improved survival.[18,19] Prior to imaging, clinical breast examination was the sole non-invasive diagnostic tool, which showed little to no evidence of benefit.[20] Modern mammography – x-ray examination of the breast – thrived from the 1970s, allowing visualisation of any associated masses, enabling earlier detection, and was shown to reduce the number of breast cancer deaths considerably.[21]

Australia's mammographic screening program, BreastScreen Australia, was established in 1991. Evidence shows the size of breast cancer detected is markedly smaller than in the period prior to screening,[22] benefiting patient prognosis. Although results are variable, it is now estimated to have reduced mortality in participants by up to 50%.[23]

Improvements in detection of cancer were powerfully bolstered by research into ultrasound, utilising sound waves in real time to form an image of internal organs, assisting to differentiate benign and malignant lesions, as well as guide fine needle aspiration of suspicious tissue.[24] Ultrasound is now used to assist diagnosis in many different types of cancers, including breast, testicular and liver.

As imaging technology continues to develop and improve, cancers will be detected earlier, providing greater treatment potential and improved outcomes.

Treatment

The 20th century saw considerable advances in the treatment of various cancers, in the 'primary triad of cancer patient care' surgery, chemotherapy and radiation,[13] in conjunction with further development of supportive and palliative care regimes.

Progress in surgery

Surgery has been a mainstay of treatment since ancient Egypt, however it is research that has propelled it from crude techniques to exploratory surgery involving laparotomy, to less invasive procedures using fiberoptic and laparosopic technology. Knowledge of cell biology and biomechanics, development of imaging modalities and refinement of surgical technique have led to procedures which are less invasive, less disfiguring and more effective at maximising removal of cancerous cells.[13] A prime demonstration of progress is the fact that clinical trials have found surgical lumpectomy with radiation equal to radical mastectomy in the management of breast cancer.[25]

Progress in chemotherapy

Medical oncology was not considered a clinical specialty even by the 1960s.[26] However, research into chemotherapy drastically changed the previously surgery-dominated field of oncology. Discovered fortuitously from research into agents of warfare, chemotherapy began with the revelation that nitrogen mustard worked against lymphoma,[27] and that by damaging DNA, rapidly dividing cancer cells could be killed.

A significant breakthrough was made in 1965 when researchers Frei, Holland and Freireich proved that a combination of chemotherapeutic drugs, each with a different mechanism of damaging DNA, could cure acute lymphoblastic leukaemia,[28] a pioneering effort that laid the foundations of modern day chemotherapeutic regimes.

This paved the way for what is now known as adjuvant chemotherapy. Comprehension of metastasis

signalled a need for change in the surgically-oriented approach to tumour management. Two landmark studies published in the mid-1970s, reporting on the effective use of adjuvant chemotherapy – one with L-phenylalanine mustard and the other a combination of cyclophosphamide, methotrexate and 5-flurouracil – with mastectomy in breast cancer patients, showed a significant decrease in relapse of patients.[29,30] It was this research that launched an intense and sustained interest in adjuvant chemotherapy, with results of decreased mortality and relapse rates we are benefitting from today. Chemotherapy is now used in a variety of solid tumour cancers, including breast, colorectal and testicular, having been credited with curing the latter,[31] and significant research continues to optimise its use.

Progress in radiation

Modern day radiotherapy involves the use of x-rays, gamma rays and charged particles to kill cancer cells and shrink tumours.[32] Radiation was first utilised to cure basal cell carcinomas of the face in 1903.[33] However, its passage into a treatment regime for cancer was interrupted by the discovery that it too caused cancer.

Research in physics and technology allowed its use in a more defined manner. Conformal radiation therapy (CRT) utilises CT images to view a cancer in three dimensions,[34] enabling more precise control of delivering the dose to the cancer, with minimal exposure to normal tissue. Intensity-modulated radiotherapy (IMRT) further builds on this, combining the precision of CRT with the ability to adjust the intensity of radiation, minimising toxicity. This has been imperative to head and neck cancer treatment, due to the proximity of important tissue to the tumour.[35] Compared to CRT, IMRT can reduce the risk of side effects such as xerostomia from damage to the salivary glands, when the head and neck are treated.[36] Evidence suggests it is effective in a variety of sites, including the prostate, and reduces toxicity to the patient.[37]

Such progress through research has meant that cancers which were previously inoperable have become curable. Today, radiotherapy is used in a wide variety of tumour types, and is part of the management of 40% of cured patients.[38]

Future direction: personalised medicine

Knowledge of the genetic basis of cancer, the Human Genome Project and further research in molecular biology and genomics has led us to an era in which we can now identify characteristics of an individual's tumour – biomarkers – in order to directly target these in treatment regimes. This is slowly transitioning oncology into a field of 'personalised medicine,' beyond the 'one size fits all' approach that previously presided.

Rational drug development, the development of drugs based on knowledge of bio-markers - is a core component of personalised medicine. It is well demonstrated by the treatment of metastatic melanoma, a disease of extremely poor prognosis and limited therapies with no survival benefit.[39] In 2002, researchers found about 50% of melanomas carry the BRAF-V600 mutation,[40] resulting in an oncogenic signalling pathway. Subsequent research delivered vemurafenib, a drug that specifically inhibits BRAF-V600, shown to significantly improve survival in patients with this mutation.[41,42] This is particularly pertinent locally, with Australia maintaining the world's highest incidence of melanomas.[43] Importantly, this remarkable research may impact on a variety of other cancer types, as the same mutation is found in thyroid, ovarian and colorectal tumours.

Hormonal therapies have long since become an integral part of personalised medicine. For example, the use of selective oestrogen receptor modulators such as tamoxifen in oestrogen and/or progesterone receptor positive breast cancers, have shown great efficacy in both suppressing recurrence and improving mortality.[44] Approximately 75% of breast cancers in Australia carry these receptors and will benefit from this therapy.

Biomarkers are increasingly used to determine individuals at risk of developing disease, and thus development of measures to prevent or reduce carcinogenesis. Individuals possessing a mutation in the adenomatous polyposis gene, at increased risk of developing colorectal cancer, can be offered endoscopic surveillance, non-steroidal anti-inflammatory drugs or, more radically, a colectomy, to help prevent occurrence. Australian researchers are now pioneering efforts to catalogue such genomic abnormalities in both pancreatic and ovarian cancers.[45]

These successes prove that increased understanding of genetic and molecular biology through research has significantly improved patient care in the field of oncology. Further research into biomarkers will guide rational drug development, expand treatment options and potential for prevention, and continue to shape the field of oncology in a more personalised direction.

Personalised medicine in Australia

The future of personalised medicine in Australia is largely dependent on current discourse regarding the economy. The National Health and Medical Research Council emphasises the increasing need to develop a balance between lowering health care costs through prevention, and the increased expense of tailored drugs produced for a small population, which major pharmaceutical companies will be more reluctant to produce.[46] Australia is moving forward in terms of educating doctors, with genetics becoming a subspecialty within the Royal Australian College of Physicians. This is increasingly important, as the role of not only management but follow-up, will be placed on oncologists and general practitioners alike, as we benefit from targeted therapy.

Application to medical education

Cancer is responsible for 10% of hospitalisations in Australia,[47] requiring regular and effective contact with junior doctors. The impact of research on clinical oncology is hence highly relevant to medical students as they prepare to enter the workforce.

The problem-based learning model of most universities in Australia allows for a diverse appreciation of clinical oncology. Cancer Council has also developed the *Ideal Oncology Curriculum*,[48] including fundamental cover of cancer biology and genomics. This is becoming increasingly important knowledge as we usher in the era of personalised medicine, with the Australia Law Reform Commission recommending comprehensive knowledge of genomics for future doctors.[49]

In the ever-changing nature of oncology, it is also crucial for students to develop competency in critically appraising the literature, in order to best apply this research for patients' benefit. These invaluable skills will serve students the breadth of their career, ensure they have knowledge that is relevant and current, and can best care for their patients.

Finally, the importance of appreciating the patient's perspective in their journey through cancer cannot be understated. Research in cancer, though significant, has further to go, and an ability to interact with, empathise, and understand patient needs is as important to effective management as knowledge of clinical oncology itself, and teaching a sound combination will ensure the best patient care is delivered.

Conclusion

Today cancer is still one of the leading causes of morbidity and mortality worldwide. However, borne out of the discoveries and developments delivered to us from research, we have improved mortality and are better equipped to support patients through their journey, progressing from 'no treatment' in ancient Egypt, to developing personalised management today.

Though it is important to recognise how far we have yet to go, it is clear the impact of developments through research has been invaluable to oncology. This research has placed us in excellent stead for continued and significant progress, overcoming challenges in the future, ever-changing, but ever-striving towards effective and comprehensive cancer control.

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BEHAVIOURAL RESEARCH AND EVALUATION UNIT (BREU), CANCER COUNCIL SA

Fear of cancer recurrence and psychological well-being in women with breast cancer: the role of causal cancer attributions and optimism

Causal attributions or beliefs that people hold with regards to the cause of their own illness are associated with affective responses to cancer and subsequent choice of coping mechanisms. This study investigated the association between causal cancer attributions, fear of cancer recurrence (FCR) and psychological wellbeing, and the possible moderating effect of optimism among women with a previous diagnosis of breast cancer.

A total of 314 breast cancer survivors (mean age = 55.22, SD = 9.33), who were diagnosed within the last five years (mean time since diagnosis = 2.89 years, SD = 1.26), completed an online self-report assessment of causal attributions for their own breast cancer, FCR, psychological wellbeing and optimism. Simultaneous multiple regression analyses were conducted to explore the overall contribution of causal attributions to FCR and psychological wellbeing separately. Hierarchical multiple regression analyses were also utilised to examine the potential moderating influence of dispositional optimism on the relationship between causal attributions and FCR and psychological wellbeing.

Results indicated that causal attributions of environmental exposures, family history and stress were significantly associated with higher FCR. The attribution of stress was also significantly associated with lower psychological wellbeing. Causal attributions of lifestyle risks and chance were not associated with psychological outcomes measured. Optimism did not moderate the relationship between causal attributions and FCR or wellbeing.

The observed relationships between causal attributions for breast cancer with FCR and psychological wellbeing among women highlight the need to improve awareness of evidence-based risk factors for breast cancer. Furthermore, health professionals may need to provide greater psychological support to women who attribute their cancer to non-modifiable causes and are less optimistic. Women who attributed the cause of their cancer to stress may be at most risk of experiencing greater distress. As beliefs about lifestyle were not associated with poorer psychological outcomes, cancer prevention messages that are intended to help women meet necessary lifestyle recommendations may help improve their cancer-related self-efficacy as opposed to exacerbating negative affective responses.

Perceptions of the solarium ban in Australia

The causal link between ultraviolet radiation from solarium use and skin cancer is well established. In 2009, the International Agency for Research on Cancer classified UV-emitting tanning devices (sunbeds) as ‘carcinogenic to humans’. Research suggests that the eradication of sunbeds from Australia would result in significant reductions in skin cancer incidence. In 2012 and 2013, state governments across Australia announced plans to ban commercial solarium use from 31 December 2014.

In 2013 and 2014, researchers from Flinders University, Cancer Councils SA and Victoria, and the University of Tasmania examined the responses of solarium users and non-users to the intended ban of commercial solariums in Australia. Participants (n = 488; 388 females, 100 males; mean age = 26.02, s.d. = 9.95) completed an online questionnaire during the summer prior to the ban relating to solarium usage and their opinions about the ban.

Results showed that 17% (n = 83) had used a solarium at some point in their life and 49% (n = 237) of participants were aware of the impending ban. The response to the solarium ban was generally positive; however, some current solarium users intended to use privately owned sunbeds post-ban or spend a greater amount of time sun-tanning.

These findings indicate a high level of public support for the solarium ban, which has removed a risky source of ultraviolet radiation in Australia. Further steps are now needed to monitor the tanning behaviours of previous solarium users post-ban and their access to private sunbed use and other potentially dangerous methods of tanning (e.g. tanning injections). More generally, application and evaluation of strategies identified in other successful public health campaign strategies (e.g. tobacco control) are required in order to ‘de-normalise’ tanning and consequently reduce UV exposure.

CENTRE FOR BEHAVIOURAL RESEARCH IN CANCER (CBRC), VICTORIA

Alcohol outlet density and adolescent alcohol consumption

As part of work conducted for the National Health and Medical Research Council Partnership project, 'How do alcohol outlet density, alcohol tax rates and alcohol advertising influence adolescents' alcohol use?', co-funded with VicHealth and FARE, CBRC has examined the association between alcohol outlet density and adolescents' alcohol use in metropolitan and regional areas in Victoria, New South Wales, Queensland, Western Australia and the Northern Territory over the period 2002 to 2011.

Alcohol consumption data were from the triennial Australian Secondary Students' Alcohol and Drug cross-sectional survey (sample size range 15,489-18,307). Postcode-level alcohol outlet density (number of licences per 1000 population) for general (hotels, pubs), on-premise (restaurants, nightclubs), off-premise (bottle shops, supermarkets) and club (social and sporting) licences were assigned to each student.

The density of general and on-premise licences was associated with drinking alcohol in the past month and drinking at risky levels (>4 drinks on one occasion in past week) for students living in metropolitan and regional areas. Off-premise outlets was related to past month alcohol use among all students, while an association with risky drinking was only found for students in metropolitan areas. Similarly, club density was associated with recent alcohol use and risky drinking for students from metropolitan, but not regional areas.

Regulating the number of general, on-premise and off-premise establishments in all communities and licensed clubs particularly in urban communities may reduce underage drinking, as a result of de-normalising drinking behaviours and exposing adolescents to fewer opportunities to access alcohol. This paper is in press in *Addiction.*

Finding the keys to successful adult-targeted advertisements on obesity prevention

Mass media communications are an important component of comprehensive interventions to address population levels of overweight and obesity. CBRC recently completed a project, funded by the Australian National Preventive Health Agency, assessing the potential effectiveness of a range of existing television advertisements pertaining to healthy weight, healthy eating and physical activity. Using a mixed-methods approach, the project aimed to provide a better understanding of the most promising content and executional styles of ads that could be pursued in obesity prevention campaigns.

Overall, the quantitative results indicated that ads emphasising the negative health consequences of excess weight appear most effective at eliciting stronger cognitive and emotional responses from adults. Further to this, the qualitative results demonstrated a fundamental need to create greater awareness of the seriousness of the health consequences of overweight and obesity, for messages with behavioural calls to action to be effective. This suggests that health effects messages (best served by visually graphic and emotionally hard hitting ads) should be the primary focus of initial obesity prevention campaigns, and that healthy eating and physical activity messages be used to support these. However, careful pre-testing of these types of ads is needed before including them in actual campaigns to ensure they do not have unintended negative impacts, such as increased stigmatisation among those who are overweight or obese.

NEWCASTLE CANCER CONTROL COLLABORATIVE (NEW-3C), NSW

Unmet needs of Australian haematological cancer survivors

Haematological cancer survivors are a unique cancer population who experience a wide range of physical, social and psychological concerns as a result of their cancer and/or treatment. To help inform relevant and appropriate care for this population, we undertook a large study assessing the psychosocial wellbeing of Australian haematological cancer survivors and their support persons. As a sub-study, we conducted a comprehensive assessment of the unmet supportive care needs of 715 haematological cancer survivors, recruited from four Australian state cancer registries. As part of this work, we established evidence of the internal consistency, face, content and convergent validity of the Survivor Unmet Needs Survey for Australian haematological cancer survivors.

Using the survey, we identified the top 10 most frequently reported 'high/very high' unmet needs items experienced by this sample. Seven of the top 10 unmet needs related to the domain of emotional health. 'Dealing with feeling tired' was the most frequently endorsed item, selected by 17% of the study sample. From this work, we also identified above normal levels of psychological distress (e.g. anxiety, depression, stress) and/or several indicators of financial burden, as characteristics associated with survivors reporting a higher overall level of 'high/very high' unmet needs, and one of the top three most frequently endorsed 'high/very high' unmet needs items.

A minority of haematological cancer survivors may require increased assistance to deal with the emotional impacts of their cancer. Survivors reporting increased psychological distress and cancer-related financial burden may be particularly susceptible to experiencing unmet supportive care needs.

Grief counselling: a systematic review of the evidence

While many individuals experience natural feelings of grief following a bereavement that resolve without need for intervention, some may need additional support, especially those experiencing complicated grief. Bereavement care incorporating grief counselling is widely offered as part of palliative care services. However, evidence for its effectiveness has been strongly debated. It is important to ensure that clinical practice is based on methodologically sound evidence, especially when limited healthcare resources are available.

A systematic review of the types of studies published about grief counselling, as well as an assessment of the quality and effectiveness of intervention studies was undertaken. While there has been a high number of studies published since 2000 reporting grief counselling interventions (76 papers), only 45 (59%) of these papers met effective practice and organisation of care design criteria. Of those 45 papers, 19 individual studies were represented, with the remaining 26 papers reporting on secondary analysis of an existing study.

Overall, intervention studies were of poor quality, with only three studies demonstrating a low risk of bias on all criteria. The effectiveness of grief counselling in these studies was mixed. There is a need for well-controlled, methodologically rigorous intervention studies of grief counselling to be conducted in order to build the evidence base for its use in palliative care. There is also scope to explore individual and social factors that may determine who is most likely to benefit from grief counselling. This review is currently in press at *Palliative Medicine.*

CANCER COUNCIL AUSTRALIA

Numbers are in: 37,000 Australians can avoid a cancer diagnosis each year

Around 37,000 Australian cancer cases could be prevented each year largely through lifestyle change, according to the first ever study of cancer incidence and preventable causes in Australia.

Published in the *Australian and New Zealand Journal of Public Health* in October, the study, funded by Cancer Council Australia and conducted by QIMR Berghofer Medical Research Institute, showed that one in three cancers in Australia could be prevented.

Cancer Council Australia CEO, Professor Sanchia Aranda, said the ground-breaking research should encourage Australians to be positive about reducing their risk.

"Of 13 identified risk factors, smoking, UV radiation, body weight, poor diet and alcohol caused around 90 per cent of all preventable cancers," Professor Aranda said. "It's time to bust the myth that everything gives you cancer and do more to reduce the risks that we know cause cancer."

Professor David Whiteman from QIMR Berghofer, who led the study, said the risk factors considered in the report had to meet three conditions: be classified by the World Health Organisation or the World Cancer Research Fund as a cause of at least one cancer type; be modifiable; and there had to be reliable data on numbers of Australians exposed to the risk factor. He said there was sufficient evidence to associate 13 different factors with 24 cancer types, including some cancers with high mortality.

"In addition to lifestyle risk factors, we analysed the impact of hepatitis B and C, human papillomavirus, HIV and Epstein Barr virus," Professor Whiteman said. "Hopefully the study will help guide lifestyle change and health policy in Australia, and contribute to the international evidence on cancer prevention."

New leadership for Cancer Council Australia

Cancer Council Australia welcomed its new CEO, Professor Sanchia Aranda, in August following the departure in 2014 of Professor Ian Olver.

Professor Aranda, previously Director of Cancer Services and Information and Deputy CEO at the Cancer Institute NSW, has had an impressive career spanning 36 years in cancer control, including as a clinician, researcher, educator and health administrator.

"I am excited to be joining Australia's leading cancer control organisation and to be able to contribute to the vital work Cancer Councils undertake to reduce the burden of cancer for all Australians through research, education, patient support and advocac," profesor Aranda said.

Professor Aranda is President-elect of the Union for International Cancer Control, Geneva, a former member of the Cancer Australia Advisory Council and Immediate Past President of the International Society of Nurses in Cancer Care. In 2013, she was awarded the Peter MacCallum Cancer Centre Distinguished Fellow.

Cancer Council also welcomed a new Chair to its Board, the Hon. Nicola Roxon, who has taken on the voluntary role for a three-year term, replacing outgoing Chair Mr Stephen Foster.

"Cancer is a community health issue I care passionately about, so it's an honour to chair the Board of Australia's pre-eminent not-for-profit cancer organisation," Ms Roxon said.

Ms Roxon is a former federal Health Minister and Attorney-General. Since her retirement from parliament in 2013, she has developed a career as a non executive director. She is currently a Director of BUPA ANZ, Chairman of the Accounting Professional and Ethical Standards Board and Chair of the Sir Zelman Cowen Centre at the Victoria University's College of Law and Justice.

Optimal Care Pathways

New guidance for health care providers is being developed in the form of Optimal Cancer Care Pathways.

In a collaboration between Cancer Council, the Federal Government through Cancer Australia and the Victorian Department of Health and Human Services, the pathways are designed to provide high-level overviews of the best cancer care a patient should receive based on available evidence. They are being produced in both detailed and quick reference versions.

PDFs of the pathways are progressively being published online at cancer.org.au/OCP. Eleven pathways are currently online, with more to be added over coming months.

Versions of the pathways are also being created for the general public, and will be made available in via a web portal.

For details, contact Jane Roy on 02 8063 4100 or email jane.roy@cancer.org.au

Cancer Council and Australian Cancer Survivorship Centre – On the Road to Recovery CALD project

Australia has one of the most culturally diverse populations in the world, with more than one in four Australians born overseas. Research has shown that culturally and linguistically diverse (CALD) migrants with cancer report higher levels of unmet needs and an inferior quality of life.

The research highlighted the the importance of providing culturally appropriate information on cancer support and services. Accordingly, the Australian Cancer Survivorship Centre at Peter MacCallum Cancer Centre joined forces with Cancer Council, to develop a booklet on cancer survivorship for the CALD community.

Funded by a Cancer Australia grant, *On the road to recovery* has been produced in Cantonese, Mandarin and Greek, and incorporates information from Cancer Council's Understanding cancer series including: *Living Well After Cancer; Emotions and Cancer; Coping with Cancer Fatigue; Cancer, Work and You; Cancer Care and Your Rights; and Understanding Complementary Therapies.*

The next stage of the project, now in development, will see versions of *On the road to recovery* produced for the Italian, Vietnamese and Arabic speaking communities.

For details, contact Jane Roy on 02 8063 4100 or email jane.roy@cancer.org.au

Decline in cancer death rates welcome, but much more to do, says Cancer Council

Data released in July shows that cancer death rates in Australia are continuing to fall, but not quickly enough, according to Cancer Council Australia.

Cancer Council Australia's Director of Public Policy, Paul Grogan, said the Australian Institute of Health and Welfare projections were based on trends showing a steady decrease in cancer deaths since the late 1960s, with a steeper drop from the late 1990s.

According to Mr Grogan, the mortality data and projections on specific tumours showed where Australia had succeeded and where more needed to be done.

"Ultimately, there is a lot more we can do as a community to improve outcomes relating to all Australians affected by cancer," he said.

Breast cancer screening rates drop, despite new data on life saving benefits

Cancer Council is encouraging all eligible Australian women aged 50 to 74 to consider participating in the free BreastScreen program following the recent release of data showing a downward trend in participation.

Figures from the Australian Institute of Health and Welfare show that BreastScreen participation rates for women aged 50 to 69 have fallen from a high of 57.6 per cent in 2001-02 to 53.7 in 2013-14.

The new data follows an analysis from the International Agency for Research on Cancer, which confirmed the life-saving benefits of screening mammography.

Newly released data also showed that Australian women's participation in cervical cancer screening has remained steady at 57.8 per cent.

Roxanne Dubash wins Cancer Council student essay competition

Medical student Roxanne Dubash, from the University of Newcastle/New England Joint Medical Program, has won the 2015 Cancer Council Australia Student Essay Competition.

Roxanne's winning essay on 'Research and the Changing Landscape of Oncology: The Journey of Cancer Control' explored the impact of science on cancer prevention, treatment and detection from the 16th Century, through to present day.

Roxanne's prize includes a trip to Vienna, Austria to attend the World Health Organisation Collaborating Centre for Cancer Education's International Summer School 'Oncology for Medical Students'.

Second place in the competition was awarded to Yiliang Zheng, while third place went to Reuben Sum. Both will receive book gift vouchers.

CLINICAL GUIDELINES NETWORK

Cancer Council Australia aims to produce concise, clinically relevant and up-to-date electronic clinical practice guidelines for health professionals. All guidelines are available on Cancer Council Australia's Cancer Guidelines Wiki platform (wiki.cancer.org.au). If you would like to be added to the mailing list for notification of guidelines open for public consultation or guideline launches, please email guidelines@cancer.org.au.

Guidelines in development

Clinical management guidelines for the prevention of cervical cancer

The Department of Health commissioned The Clinical Guidelines Network to develop new evidence-based clinical management guidelines for the prevention of cervical cancer in order to support the implementation of the renewed National Cervical Screening Program. The working party convened in August and the systematic reviews and modelled evaluations are currently being conducted by a technical team based at Cancer Council NSW.

Clinical practice guidelines for PSA testing and management of test-detected prostate cancer

The guidelines are currently with the National Health and Medical Research Council for approval. Once finalised, the guidelines will be formally launched.

Clinical practice guidelines for the prevention, diagnosis and management of lung cancer

Cancer Council is currently developing prevention and diagnosis guidelines for lung cancer to complement the treatment guidelines. Systematic reviews for the diagnosis questions are currently being conducted.

Clinical practice guidelines for the diagnosis and management of melanoma

Cancer Council and Melanoma Institute Australia have started to revise the 2008 melanoma guidelines as online wiki-based guidelines. Systematic reviews and systematic review updates are currently being conducted.

Clinical practice guidelines for the prevention, early detection and management of colorectal cancer

Revision of the 2005 *Clinical practice guidelines for the prevention, early detection and management of colorectal cancer* is underway. The initial working party meeting was held in June and the systematic reviews are currently being conducted.

Clinical practice guidelines for the management of sarcoma in AYA

Additional questions relevant to the AYA population are currently being added to the sarcoma guidelines.

Cancer Council Australia Guidelines on the wiki

Cancer Council's Cancer Guidelines Wiki features the following cancer-based guidelines:

- *Clinical practice guidelines for the diagnosis and management of Barrett's Oesophagus and Early Oesophageal Adenocarcinoma*
- *Clinical practice guidelines for the treatment of lung cancer*
- *Management of apparent early stage endometrial cancer*
- *Clinical practice guidelines for surveillance colonoscopy*
- *Clinical practice guidelines for the management of adult onset sarcoma*
- *Clinical Practice guidelines for the management of locally advanced and metastatic prostate cancer*

Clinical Oncology Society of Australia guidelines hosted on the wiki:

- NETs guidelines
- Head and neck cancer nutrition guidelines
- Early detection of cancer in AYAs
- AYA cancer fertility preservation
- Psychosocial management of AYA cancer patients
- Cancer pain management

For more information contact the Head, Clinical Guidelines on 02 8063 4100 or email guidelines@cancer.org.au.

CLINICAL ONCOLOGY SOCIETY OF AUSTRALIA, COSA

COSA Annual Scientific Meeting (ASM)

2015 COSA ASM – Hobart

The 42nd COSA ASM will be held in Hobart, 17-19 November 2015, at the Hotel Grand Chancellor. The full detailed program is available online cosa2015.org. Please check the website regularly for information about registration, speakers and program updates.

The opening plenary on Tuesday will set the scene to define what rare cancers are, how we classify them, how we diagnose and treat them, and how patients cope with them. The second plenary features a talk on three common rare cancers – sarcoma, neuroendocrine tumours and rare melanoma, followed by a concurrent session on each that will investigate each disease in more detail. As well as hearing from various health professional experts, the sarcoma and NETs sessions will both include talks from patients.

Luke Ryan is a Melbourne-based writer, comedian and two-time recipient of a sarcoma by the time he was 22 - an osteosarcoma at 11, followed by an undifferentiated pleomorphic sarcoma exactly 11 years later. It's a medical history of such obscurity that his oncologist once referred to him as a 'data-free zone' and then made a crack about shooting in the dark. Luke has written and spoken about his experiences extensively, both in his 2014 book *A Funny Thing Happened on the Way to Chemo* and through a stand-up career that began while he was having treatment in 2008.

Simone Leyden is CEO and co-founder of the Unicorn Foundation Australia and New Zealand, a not-for-profit medical charity directed towards neuroendocrine cancers. In her role as CEO, Simone concentrates on rare cancer patient advocacy, fundraising, marketing, managing volunteers and managing the paid specialist NET Nurse, who among other roles runs the Unicorn Foundation telephone and internet support service.

2016 COSA ASM – Gold Coast

COSA is partnering with the ANZ Breast Cancer Trials Group to host a joint breast cancer focused conference, 15-17 November 2016 at the Gold Coast Convention and Exhibition Centre.

2017 COSA ASM – Sydney

We are currently in negotiations with the new International Convention Centre to host the 2017 COSA ASM in Sydney. The Sydney Convention Centre was demolished and construction has begun, with the planned opening of the new centre in December 2016 – plenty of time for them to iron out the creases to welcome us in November 2017.

2018 COSA ASM – Perth

13-15 November 2018 at the Perth Convention and Exhibition Centre. Please diarise now.

Working with Cancer Council Australia

In COSA's role as medical and scientific advisors to Cancer Council Australia, we often collaborate on submissions to government. In 2015, we have submitted the following joint submissions from Cancer Council Australia and COSA:

1. Review of Medicines and Medical Devices Regulation – Cancer Council/COSA recommendations to the Australian Government (February 2015).
2. Senate inquiry into the availability of new, innovative and specialist cancer drugs in Australia (February 2015).
3. Response to a Bill for an Act to establish the Regulator of Medicinal Cannabis, and for related purposes (March 2015).
4. Therapeutic Goods Administration Orphan Drugs Program: Discussion paper (March 2015).
5. Inquiry into Chronic Disease Prevention and Management in Primary Health Care (July 2015).

For more information about COSA activities please visit www.cosa.org.au

Marie Malica
Executive Officer, COSA

FACULTY OF RADIATION ONCOLOGY, RANZCR

Radiation Oncology Targeting Cancer campaign

Lack of awareness of radiation therapy's value in treating cancer has been a long standing problem. Raising the profile of radiation oncology remains a major priority for the Faculty. We will continue the work in this area through the Radiation Oncology: Targeting Cancer campaign, which reached more than 7.5 million people in the 2014/15 financial year.

The Targeting Cancer website has been designed to provide relevant and timely information to patients and their loved ones, as well as health professionals. While content is focused mainly on information of relevance to people in Australia and New Zealand, the website receives significant interest from viewers overseas and is averaging 756 unique visitors per month.

The Targeting Cancer community service announcement/ short film - Targets showcases radiation therapy by highlighting the stories of real patients who have received this treatment. By sharing their different experiences, we hope to connect with patients and their loved ones who are currently considering treatment options. The short film has been shown around the world, including at meetings of the American Society for Radiation Oncology and the European Society for Radiotherapy and Oncology.

Referrals from other medical professionals, such as general practitioners (GPs), are also critical to achieving the campaign's objective – to ensure that cancer patients who might benefit from radiation therapy know about it and receive it. To reach GPs, the campaign supports the planning and delivery of clinician-hosted oncology education evenings which demystify radiation therapy, address common scenarios that referrers encounter, and connect referrers to cancer centres.

Social, digital and print media round out the campaign's main channels for engaging with audiences and communicating important information.

Please continue to support us in this important initiative to raise the profile of radiation oncology in any or all of the following ways:

- Visit the website and register your support.
- Follow the campaign on Twitter (@TargetingCancer).
- Visit and 'like' the Facebook page.
- Connect to the campaign on LinkedIn.
- Email us your ideas and suggestions for media stories to help drive traffic to the website.

Advocacy to ensure prostate cancer patients are informed about all treatment options

Every year, around 20,000 Australian men are diagnosed with prostate cancer. While surgery has long been regarded as the most effective treatment option, modern radiation therapy has been shown to be just as successful. International guidelines consider both treatment options as appropriate in the management of localised prostate cancer, and recommend that both options be discussed with patients.

There was a recent debate between A/Prof Sandra Turner, a Senior Radiation Oncologist from Westmead Hospital with urologist Professor Mark Frydenberg on ABC Lateline. This has opened broader debate. The Faculty hopes to work constructively with all stakeholders to ensure joint position statements can be developed as well as on other collaborative initiatives.

Funding for radiation oncology

The Faculty holds the view that cancer patients must have adequate and timely access to appropriate radiation therapy treatments. In the past 12 months, we have been actively negotiating with the Department of Health (DoH) in Australia on the Medical Services Advisory Committee (MSAC) applications for Intensity modulated radiation therapy (IMRT) and image guided radiation therapy (IGRT).

Following continuous negotiations, it is likely that IMRT and IGRT will be listed on the Medicare Benefits Schedule, with separate items to support further data collection on utilisation and cost effectiveness, under the condition that it is cost-neutral. Though not an ideal outcome, we believe it is a big step forward that the modern techniques benefiting cancer patients are at least recognised, in the hope that they will be appropriately reimbursed in the future.

While the Faculty commends the MSAC for developing an item number of IMRT and IGRT, we are disappointed with the MSAC process, which shows a lack of understanding of radiation therapy, and a lack of appropriate consultation. The Faculty will actively participate in the current review of the MSAC process by the Australian Government, to help ensure a more evidence-based approach and appropriate assessment of medical services in the future.

The Australian Government recently announced a review and restructure of Medicare Benefits Schedule. The Faculty welcomes this opportunity to modernise the way radiation therapy is funded, and trust that the ultimate outcome will be beneficial for cancer patients.

Dr Dion Forstner
Dean, Faculty of Radiation Oncology, RANZCR

MEDICAL ONCOLOGY GROUP OF AUSTRALIA INCORPORATED, MOGA

2015 has proven to be a challenging, dynamic and profitable year for the Association.

Workforce issues

The medical oncology workforce has been an ongoing focus of our activities. The NSW Health Department conducted a Junior Medical Officer Recruitment Strategy Review in June to identify major future risks and challenges, particularly with regard to changes resulting from increased workforce supply. In addition to developing a submission in response to this Review, the MOGA Workforce Taskforce led by Dr Zarnie Lwin, finalised a Workforce pilot protocol. The purpose of this project is to gather information that can be used to address identified workforce issues.

The Royal Australasian College of Physicians is also proceeding with workforce matters across all its specialities. In response to the College's capacity to train-consultation paper, a recent MOGA submission identified issues in the wider health context that may impact capacity to train, including: the increasing survival rate of patients with cancer, requiring longer term treatment and care; the increasing levels of specialisation and sub-subspecialties in medical oncology practice; the increasing complexity and number of medical oncology therapies and clinical options; predicted increases in chemotherapy utilisation in Australia; and the increasing cost, complexity and length of training requirements for medical oncology. MOGA's submission also detailed recommendations on actions and strategies to be adopted to mitigate risk and maximise the advantages of various approaches to the resolution of workforce planning issues.

Oncology drugs and treatments

Following the Community Affairs References Committee 2014-15 Inquiry into new, innovative and specialist cancer drugs, the Senate held a public hearing in April. MOGA was called to present and was represented by Dr Christopher Steer. MOGA also welcomed the federal budget announcements regarding: early access to superannuation options for the terminally ill; PBS funding for new drugs for breast, colorectal and melanoma cancers; and $400M for researchers via the Medical Research Future Fund. Major oncology drugs and treatment issues that have been on MOGA's agenda include: biosimilars in the Australian marketplace; the government's pharmacy payment package that it is hoped will provide medicinal compounders with the certainty needed to continue to deliver chemotherapy drugs on demand to patients and doctors; and advocating for access to oncology drugs going through for PBS listing.

EVOLVE Project

MOGA has established a new working group, Chaired by Associate Professor Winston Liauw, to identify low value interventions used in Australian medical oncology practice as part of the Royal Australasian College of Physicians' EVOLVE project. Associate Professor Liauw is the Director Cancer Services South Eastern Sydney Local Health District and Conjoint Associate Professor UNSW. As a medical oncologist, clinical pharmacologist and a Board member of NPS MedicineWise, he is well placed to lead this project. The other members of the group include: Professor Bogda Koczwara; Dr George Au-Yeung; Dr Susie Bae; Dr Pretoria Bilinski; Dr Adrian Lee; Dr Miles Andrews; and Dr Sanjana Kondola. Professor Derek Raghavan (President, Levine Cancer Institute, Carolinas HealthCare System; Professor/ Medicine, UNC School of Medicine) will also assist given his expertise with the ASCO Value Task Force Advice Committee. The working group is currently developing a project plan and reviewing the Canadian and US models for Choosing Wisely.

MOGA 2015 ASM Hobart, Tasmania

The MOGA 2015 Annual Scientific Meeting, 'Pathways in Medical Oncology: The Path Less Travelled,' explored many of the contemporary challenges and advances in medical oncology research, discovery and clinical practice in breast, melanoma, lung and gynaecological cancer. International guest speakers included Professor Fatima Cardoso (Portugal), Professor Chih-Hsin James Yang (Taiwan), Professor Adil Daud (US) and Professor Hani Gabra (UK). The program also focused on lesser covered areas such as head and neck cancer and haematological malignancies. Presentations from Australian specialists also took paths less travelled - Professor Bogda Koczwara convened a Forum on 'Emerging Challenges of Cancer Survivorship' and Professor Stewart Dunn and Professor Fran Boyle convened a Forum on 'Difficult Conversations: Sex, Death, Money and Error'.

Associate Professor Rosemary Harrup
Chair, Medical Oncology Group of Australia Incorporated

THE ROYAL AUSTRALASIAN COLLEGE OF PHYSICIANS' CONGRESS, MAY 2015

Cairns was the host city for the 2015 Royal Australasian College of Physicians' Congress 'Breaking Boundaries and Creating Connections', an opportunity to delay winter while inspiring and expanding the mind.

Plenaries addressed a wide range of topics, including refugee and asylum seeker health, origins of clinical governance, medicine in Madagascar, the conundrum of consumer driven care, the persistent disparity in health care between first peoples and non-indigenous populations, and contrasting the depths and peaks of modern medicine, challenging us to provide excellent and compassionate care. Updates were offered on wide ranging topics such as Ebola, sleep, amyloidosis, genetics, integrated care, gender dysphoria, and faecal microbiota transplantation.

This report summarises presentations at the Congress on 'end of life care'.

There were opportunities to meet physicians and trainees from both sides of the Tasman, students through to retiring physicians, to break barriers to the conversations about palliative care and the inevitability of end of life, encouraging collaborative care, respecting and responding to community expectations, and accepting the limitations of resources. There was a sense that while the science and politics of health are clamouring for attention, the art of medicine persists.

Intensive care unit physician, A/Prof William Sylvester, discussed advanced care planning, from Hippocrates with beneficence and nonmaleficience, to modern goals of respecting autonomy, informed consent, dignity and prevention of suffering. Conversations about acceptable outcomes for quality of life are easier to broach, more useful than specifics of care, and can be aligned with treatment options and prognosis. Establishing and documenting surrogate decision makers is important. A randomised controlled trial on advanced care planning was statistically significant for knowing end of life care wishes, patients and families being more satisfied with end of life care, and reduction in stress, anxiety and depression in families at three months. This empowers patients now, not just in the future, can be used in patients with dementia and aligns with religious and ethical principles.

The managing end of life support panel discussion addressed aspects such as: who cares for the dying; when to refer to palliative care; need for training in all specialties; ATSI and CALD cultural competency needs a team approach; cannabis for symptom relief; terminal sedation and voluntary palliated starvation indicating clinician's helplessness vs patient suffering; and disability does not imply distress or a wish for death. The goal is to relieve suffering and regain dignity.

Dr Frank Brennan, palliative care physician pivotal in establishing renal supportive care at St George Hospital Kogarah, outlined many barriers to and myths about palliative care. The definition of palliative care (WHO 2002) addresses care in life-threatening illness, not only cancer. Palliative care principles can be applied across many disciplines, e.g. end stage organ failure and motor neurone disease, extending experience gained from care of cancer patients. Balancing with acute management, often essential to good symptom control, is complex. Recognising when diseases are life-limiting allows end of life discussions and appropriate care. Limited palliative care resources and uncertain prognostication in non-malignant disease trajectories necessitate a combined approach. Palliative care provides a real alternative to active management.

Other sessions expanded on advanced planning, the rights of the child at end of life, the parents' role in decision making and compassionate medicinal cannabis in Canada.

Dr Vanessa Tung
Palliative Medicine Staff Specialist Calvary Health Care Kogarah

AUSTRALIA AND NEW ZEALAND

Date	Name of Meeting	Place	Secretariat
November			
6-7	Melanoma Summit 2015	Auckland, New Zealand	MelNet Website: www.melnet.org.nz/news/melanoma-summit-2015 Email: melnet@melnet.org.nz Phone: 0274 715 931
10-13	ALLG Scientific Meeting	Melbourne, Victoria	Australasian Leukaemia & Lymphoma group Website: www.allg.org.au Email: dilupa.uduwela@allg.org.au +61 3 8373 9702
16-17	Research Administrators' Seminar	Canberra, Australian Capital Territory	NHMRC Website: www.nhmrc.gov.au/media/events/2015/research-administrators-seminar-2015 Email: reservations@realmprecinct.com.au Phone: +61 2 6163 1800
17-19	Clinical Oncology Society of Australia's (COSA) Annual Scientific Meeting 2015	Hobart, Tasmania	ASN Events Pty Ltd Website: www.asnevents.net.au Email: eg@asnevents.net.au Phone: +61 3 5983 2400
21	2015 Sydney Colorectal Surgical Meeting	Sydney, New South Wales	Royal Australasian College of Surgeons Website: www.eventspro.net/surgeons/getdemo.ei?id=7010070&s=_ESJ9NUU4C Email: colorecal.sm@surgeons.org Phone: +61 3 9276 7406
December			
1-2	Inaugural Australasian Youth Cancer Summit	Sydney, New South Wales	Chillifox events Website: www.youthcancerevent.com.au/summit Email: youthsummit@chillifoxevents.com.au Phone: +61 2 8005 1867
3-5	Inaugural International Adolescent and Young Adult (AYA) Oncology Congress	Sydney, New South Wales	Chillifox events Website: www.youthcancerevent.com.au/summit Email: ayacongress@chillifoxevents.com.au Phone: +61 2 8005 1867
9-11	3rd International Conference on UV and Skin Cancer Prevention	Melbourne, Victoria	Arinex Pty Ltd Website: www.uvandskincancer2015.org Email: uv2015@arinex.com.au Phone: +61 2 9265 0700
2016			
February			
11-13	28th Lorne Cancer Conference	Lorne, Victoria	ASN Events Pty Ltd Website: www.lornecancerss3.asnevents.com.au/ Email: eg@asnevents.net.au Phone: +61 3 5983 2400
March			
13-16	Australian Pain Society 36th Annual Scientific Meeting	Perth, Western Australia	DC Conferences Pty Ltd Website: www.dcconferences.com.au/aps2016/ Email: aps2016@dcconferences.com.au Phone: +61 2 9954 4400

14-17	TROG Annual Scientific Meeting	Brisbane, Queensland	TROG Cancer Research Website: www.trog.com.au Email: TBC Phone: TBC
April			
12-15	8th General Assembly and International Conference of the Asian Pacific Organisation for Cancer Prevention	Brisbane, Australia	Carillon Conference Management Pty Ltd Website: www.apocp8.org Email: admin@ccm.com.au Phone: + 61 7 3368 2644
May			
2-6	Royal Australasian College of Surgeons Annual Scientific Meeting 2016	Cairns, Queensland	Royal Australasian College of Surgeons Website: www.asc.surgeons.org/ Email: asc.registration@surgeons.org Phone: +61 3 9276 7431
12-14	CNSA 19th Annual Congress	Melbourne, Victoria	CNSA Website: www.cnsa.org.au Email: info@cnsa.org.au Phone: +61 4 1982 2969
26-28	Asian Pacific Lymphology Conference	Darwin, Northern Territory	Australasian Lymphology Association Website: www.lymphoedema.org.au Email: admin@lymphoedema.org.au Phone: +61 3 9586 6030

INTERNATIONAL

Date	Name of Meeting	Place	Secretariat
November			
5-7	Advanced Breast Cancer 3rd International Consensus Conference (ABC3	Lisbon, Portugal	European School of Oncology (ESO) Website: www.abc-lisbon.org Email: eso@eso.net Phone: +351 21 415 6120
6-7	1st International Hematology Club Meeting: a focus on lymphoid diseases (IHC)	Paris, France	ComtecMed Website: www.comtecmed.com/ihc/2015/ Email: IHC@comtecmed.com Phone: +972 3 5666166
12-14	International Society of Geriatric Oncology (SIOG)	Prague, Czech Republic	SIOG Website: www.siog.org/ Email: info@siog.org Phone: +41 22 552 3305
18-22	Aortic 2015 International Cancer Conference	Marrakech, Morocco	African Agenda Website: www.aorticconference.org Email: info@aorticconference.org Phone: +27 (0)21 683 2934
December			
3-6	5th International Gastrointestinal Cancers Conference (IGICC 2015)	Istanbul, Turkey	Serenas Tourism Congress Organization and Hotel Management Co. Website: www.igicc2015.org Email: igicc2015@serenas.com.tr Phone: +90 312 440 50 11

8-12	38th Annual San Antonio Breast Cancer Symposium	San Antonio, Texas	Richard Markow Website: www.sabcs.org Email: sabcs@uthscsa.edu Phone: 210-450-1550
18-21	ESMO Asia Congress 2015	Singapore	ESMO Website: www.esmo.org/Conferences/ESMO-Asia-2015-Congress/ Email: esmo@esmo.org Phone: +41 (0)91 973 19 00
2016			
January			
22-23	2016 Progress and Controversies in Gynecologic Oncology Conference	Barcelona, Spain	prIME Oncology Website: www.primeoncology.org/gyncongress2016 Email: gyncongress2016@prIMEoncology.org Phone: +31 70 30 67 190
March			
10-12	3rd St Gallen International Gastrointestinal Cancer Conference	St Gallen, Switzerland	St.Gallen Oncology Conferences Website: www.oncoconferences.ch Email: info@oncoconferences.ch Phone: +41 (0)71 245 68 05
April			
13-16	6th European Lung Cancer Conference (ELCC)	Geneva, Switzerland	ESMO Website: www.esmo.org/Conferences/ELCC-2016-Lung-Cancer Email: esmo@esmo.org Phone: +41 (0)91 973 19 00
17-20	International Symposium on Oncology Pharmacy Practice)	Santiago, Chile	Sea to Sky Meeting Management Inc. Website: www.isopp.org/isopp-symposia/isopp-2016/contact Email: symposium@isopp.org Phone: +1 604 984 6455
28-30	2nd World Congress on Controversies in Multiple Myeloma (COMy)	Paris, France	ComtecMed Website: www.comtecmed.com/comy/2016/ Email: info@comtecmed.com Phone: +972 3 5666166
May			
6-7	1st International eCancer Symposium on Radiotherapy	Santiago, Chile	eCancer Website: www.ecancerchile.com Email: samantha@ecancer.org Phone: TBC
June			
3-7	ASCO 52nd Annual Scientific Meeting	Chicago, USA	ASCO Website: www.am.asco.org/ Email: TBC Phone: TBC
6-10	IARC 50th Anniversary Conference	Lyon, France	IARC Website: www.iarc-conference2016.com/ Email: iarc2016@inviteo.fr Phone: +33 825 595 525

CANCER COUNCIL AUSTRALIA

Cancer Council Australia is the nation's peak independent cancer control organisation.

Its members are the leading state and territory Cancer Councils, working together to undertake and fund cancer research, prevent and control cancer and provide information and support for people affected by cancer.

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The Clinical Oncology Society of Australia (COSA) is a multidisciplinary society for health professionals working in cancer research or the treatment, rehabilitation or palliation of cancer patients.

It conducts an annual scientific meeting, seminars and educational activities related to current cancer issues. COSA is affiliated with Cancer Council Australia.

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Cancer Forum provides an avenue for communication between all those involved in cancer control and seeks to promote contact across disciplinary barriers. To this end, articles need to be comprehensible to as wide a section of the readership as possible. Authors should provide sufficient introductory material to place their articles in context for those outside their field of specialisation. *Cancer Forum* is primarily a review journal, with each issue addressing a particular topic in its 'Forum'. The Forum topic and appointment of Guest Editor(s) are determined by the Editorial Board, which welcomes suggestions. Proffered papers containing primary research findings will be considered for publication in *Cancer Forum* in limited circumstances. Articles will be considered by the Editorial Board and then published subject to two peer-reviews. Generally speaking, authors are encouraged to submit their primary research findings to established cancer research or clinical oncology journals. The following information is provided for contributors invited to prepare manuscripts for *Cancer Forum*.

Format

Prospective authors are encouraged to examine recent editions of *Cancer Forum* for an indication of the style and layout of Forum papers (cancerforum.org.au). All manuscripts should be submitted by email to the Forum's Guest Editor(s) and Executive Editor (rosannah.snelson@cancer.org.au) as MS Word documents.

Length: 2000-2500 words.

Font: Arial - 20pt and bold for title, 12pt and bold for headings, 12pt and italics for subheadings and 10pt for text.

Following the title, include your full name, organisation and email address. Include introductory headings and sub-headings that describe the content. Number pages in the footer.

Abstract

All manuscripts must include an abstract of approximately 200 words, providing a summary of the key findings or statements. No references or abbreviations should be included in the abstract.

Abbreviations and acronyms

Abbreviations and acronyms should only be used where the term appears more than five times within the paper. They must be explained in full in the first instance, with the abbreviation in brackets. The Editorial Board reserves the right to remove the heavy use of abbreviations and acronyms that may be confusing to the diversity of our readership.

Photographs, tables and graphs

Photographs and line drawings can be submitted via email, preferably in jpeg format. If images are not owned by the author, written permission to reproduce the images should be provided with the submission. A maximum of five illustrations and figures and three tables can be submitted with the manuscript. Inclusion of additional items is subject to approval by the Editorial Board. Unless otherwise specified by the authors or requested by the Editorial Board, all images, graphs and tables will be printed in black and white. All figures – including tables and graphs – will be reproduced to *Cancer Forum's* style. Figures containing data (e.g. a line graph) must be submitted with corresponding data so our designers can accurately represent the information. Figures and images should be labelled sequentially, numbered and cited in the text in the correct order e.g. (table 3, figure 1). Tables should only be used to present essential data. Each must be on a separate page with a title or caption and be clearly labelled.

Referencing

Reference numbers within the text should be placed after punctuation and superscripted. The maximum number of references is 75. Only papers closely related to the subject under review should be quoted and exhaustive lists should be avoided. Only one publication can be listed for each number. Citation of more than one reference to make a point is not recommended. The Editorial Board prefers a focus on more recent references (in the last 10 years). The list of references at the end of the paper should be numbered consecutively in the order in which they are first mentioned and be consistent with the National Library of Medicine's International Committee of Medical Journal Editors' Uniform Requirements for Manuscripts Submitted to Biomedical Journals. i.e. Halpern SD, Ubel PA, Caplan AL. Solid-organ transplantation in HIV-infected patients. N Engl J Med. 2002 Jul 25;347(4):284-7.

The Editorial Board will make the final decision on inclusion of manuscripts and may request clarifications or additional information.

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