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Program for the treatment of locally advanced prostate cancer.

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PRIORITISING SUMMARY

REGISTER ID: **000181**

NAME OF TECHNOLOGY: **PROGRAM FOR THE TREATMENT OF PROSTATE CANCER**

PURPOSE AND TARGET GROUP: **TREATMENT OF LOCALLY ADVANCED PROSTATE CANCER IN MEN**

STAGE OF DEVELOPMENT (IN AUSTRALIA):

☐	Yet to emerge	☐	Established
☐	Experimental	☐	Established *but* changed indication or modification of technique
☐	Investigational	☐	Should be taken out of use
☒	Nearly established		

AUSTRALIAN THERAPEUTIC GOODS ADMINISTRATION APPROVAL

☐	Yes	ARTG number
☐	No	
☒	Not applicable	

INTERNATIONAL UTILISATION:

COUNTRY	LEVEL OF USE		
	Trials Underway or Completed	Limited Use	Widely Diffused
Australia	✓		
New Zealand	✓		

IMPACT SUMMARY:

This prioritising summary investigates the effectiveness of using hormone therapy prior to radiotherapy in the treatment of locally advanced prostate cancer.

BACKGROUND

There are a number of techniques currently available for the treatment of localised prostate cancer. Treatment options include prostatectomy, radiotherapy, hormonal therapy, cryotherapy and watchful waiting. Which of these treatment options is optimal for a particular patient can often depend on a variety of factors, including the patient's age, general health, disease progression and prostate specific antigen (PSA) levels. The choice of treatment can also depend on the patient's views on possible risks and side effects (such as bowel problems or loss of sexual function), and the effect the treatment technique will have on overall lifestyle. Radiotherapy has become the preferred method for treating localised prostate cancer when the risks associated with prostatectomy are too high. Candidates for radiotherapy are generally older than patients receiving prostatectomy, and subsequently have a poorer cancer-specific prognosis (NHRMC, 2003).

A number of small studies have suggested that short-term hormonal therapy given prior and during radiotherapy can improve outcomes in men with locally advanced prostate cancer. Hormonal therapy aims to reduce the size of the tumour, making subsequent radiotherapy more effective. Laverdiere et al (1997) found that either three or six months of androgen deprivation prior to radiotherapy improved local disease control two years after treatment relative to radiotherapy alone. Another study by Pilepich et al (2001) found that four months of androgen deprivation before and during radiotherapy improved outcomes on all measures, including survival rates and local disease control. Unfortunately, these and other similar trials have not adequately shown which patients benefit from hormonal therapy, for how long the therapy should be continued, and what improvements in outcome can be expected.

This prioritising summary describes a recent large scale study conducted in Australia and New Zealand that has provided much stronger evidence for the use of hormonal therapy prior to radiotherapy.

CLINICAL NEED AND BURDEN OF DISEASE

In Australia, prostate cancer is the second most common form of cancer in men, behind only skin cancer. In 2001, prostate cancer was responsible for 23 per cent of new cancer diagnoses, with 11,191 men in total being diagnosed with the disease (AIHWa, 2005). In 2003, 20,547 public hospital separations for prostate cancer were recorded, with an average length of stay of 4.7 days (AIHWb, 2005). Similar statistics have also been reported in New Zealand. In 2001, 3046 prostate cancer registrations were reported, which accounted for 31.9 per cent of total cancer registrations in New Zealand that year (NZHIS, 2005).

Of the men diagnosed with prostate cancer each year, it is estimated that approximately 4000 Australians and 800 New Zealanders are diagnosed with localised prostate cancer that is too advanced for prostatectomy to be effective or safe (TROG, 2005). Radiotherapy becomes one of the primary treatment options for these men.

The most significant risk factor for prostate cancer is age. More than half of all new prostate cancer cases occur in men over the age of 70 (APCC, 2003). In 2001, 86% of new prostate cancer cases in Australia were reported in men over the age of 60 (AIHWa, 2005). Similarly, in New Zealand, 90% of all discharges from public and private hospitals in 2001 were for men over the age of 60 (NZHIS, 2005).

Relative to many other forms of cancer, the progression from diagnosis to death for prostate cancer victims is prolonged. In Australia, the five year survival rate for men diagnosed with prostate cancer is estimated to be approximately 83 per cent (AIHW, 2001). Between 1998 and 2002, the median age of death for victims of prostate cancer was 78 years, older than for any other type of cancer (AIHW, 2002). Although these survival trends compare favourably to other forms of cancer, prostate cancer is still the second leading cause of cancer related death in Australian men. In 2001, a total of 2718 males died of prostate cancer, making up over 13 per cent of total male cancer deaths that year (AIHW, 2004). Only lung cancer was responsible for a greater number of deaths. The median age at death for prostate cancer victims was 78 years between 1998 and 2002. Similar mortality patterns have also been reported in New Zealand, where a total of 592 men (14 per cent of total cancer related deaths) died of prostate cancer in 2001 (NZHIS, 2005).

DIFFUSION

According to the National Health and Medical Research Council, it is becoming more common for hormone therapy to be given prior to radiotherapy to reduce tumour size (NHMRC, 2003). However this combination of treatments is not considered to be standard practice in the treatment of locally advanced prostate cancer (NHMRC, 2003). In any case, there is little information indicating precisely how many practitioners are offering this

treatment within Australia and New Zealand, and what the average length of hormonal therapy has been.

COMPARATORS

Alternative treatments for localised prostate cancer include radiotherapy and hormonal therapy on their own, prostatectomy, cryotherapy and watchful waiting. In cases where the cancer is more advanced (but still localised) and the patient has a poorer prognosis, radiotherapy or watchful waiting are typically the most appropriate treatment choices. Watchful waiting, in which no treatment is administered, is suitable for patients whose life expectancy is less than 10 years and who prefer to avoid the side effects of other treatment methods. Radiotherapy on the other hand is suitable for patients whose life expectancy exceeds 10 years (in the absence of the cancer) and who accept the risks associated with the treatment. Long-term side effects of radiotherapy include erectile dysfunction, and less commonly bowel problems and urinary incontinence (NHRMC, 2003).

EFFECTIVENESS AND SAFETY ISSUES

A recent large scale trial by Denham et al (2005) (level II intervention evidence), on behalf of the Trans-Tasman Radiation Oncology Group, investigated the use of hormonal therapy prior to radiotherapy. The multicentre study involved 818 Australian and New Zealand men, all diagnosed with locally advanced prostate cancer. The men were randomly assigned to receive either radiotherapy alone (the standard treatment), or radiotherapy following a three or six month period of androgen deprivation. Androgen deprivation involved giving patients 3.6mg goserelin subcutaneously once per month in addition to patients taking an oral dose of 250mg flutamide three times a day.

Primary outcomes for the study included local failure and prostate-cancer-specific survival. Local failure was defined as the time to tumour recurrence, or in cases where the primary tumour never disappeared, was defined as occurring at random. In measuring prostate-cancer-specific survival, death was attributed to prostate cancer if the patient had progressive prostate cancer, otherwise the observation was censored. Secondary outcomes included distant failure, biochemical failure, disease-free survival and freedom from salvage treatment of any type for a recurrence. Distant failure was defined as metastasis at sites outside the prostatic region, while biochemical failure referred to an increase in PSA of at least 2 μg/L following radiotherapy. Finally, disease-free survival referred to the time until the first evidence of clinical failure at any anatomical site, biochemical failure, or death from any cause.

Results from the study demonstrated that both three and six months of androgen deprivation before and during radiotherapy greatly improves patient outlook. Compared with patients who received the standard treatment, patients who received three months androgen deprivation reported significantly lower local failure rates ($HR = 0.56$, $p = 0.001$). Biochemical failure-free survival, disease-free survival and freedom from salvage treatment were also significantly improved in patients who received three months androgen deprivation. Similarly, patients who received six months androgen deprivation reported significantly lower local failure rates ($HR = 0.42$, $p < 0.001$) and prostate-cancer-specific failure rates ($HR = 0.56$, $p = 0.04$) than patients who received no androgen deprivation. That is, six months of androgen deprivation more than halved prostate cancer relapses and reduced deaths attributable to the cancer by more than 40%. All secondary outcomes were also significantly improved in patients who received the six months of androgen deprivation. While there were no significant differences in outcomes reported between the two androgen deprivation groups, the authors recommend six months androgen deprivation as the appropriate length of treatment for improving patient outcomes.

In an earlier report from the same study, Christie et al (2005) examined the effects of three and six month's androgen deprivation prior to and during radiotherapy on rectal and urinary

function. It was found that both three and six months of androgen deprivation had little or no impact on the prevalence or time to occurrence of delayed urinary dysfunction. Furthermore, it was found that three months androgen deprivation led to a modest decrease in the time to and occurrence of delayed proctopathy compared with six months androgen deprivation and radiotherapy alone.

COST IMPACT

The additional costs of hormone therapy prior to and during radiotherapy arise from the antiandrogens that are prescribed. In Australia one dose of goserelin (3.6mg) costs $341.83 (PBS item number 1454M), while 100 doses of flutamide (250mg) cost $221.83 (PBS item number 1417N). As a result, the cost of three months hormone therapy using this combination of antiandrogens (goserelin once per month and flutamide three times daily) would be $1690.98, while six months hormone therapy would cost $3381.96.

At this stage there are no documented reports on the average costs of follow-up treatment for patients who have received radiotherapy in the treatment of locally advanced prostate cancer. It is likely however that reductions in the recurrence and spread of prostate cancer following a program of additional hormone therapy would produce significant cost savings for the health system.

ETHICAL, CULTURAL OR RELIGIOUS CONSIDERATIONS

No issues were identified/raised in the sources examined.

OTHER ISSUES

Following the promising results reported in their study, the Trans-Tasman Radiation Oncology Group (TROG) has begun a new large scale study known as RADAR. The RADAR study has been designed to test whether 18 months of hormone therapy in addition to radiotherapy improves outcomes when compared to 6 months hormone therapy prior to and during radiotherapy. The study is also testing the effectiveness of a new bisphosphonate (called Zometa or zoledronate) which has the potential to prevent the bone loss or destruction that is associated with hormone therapy.

CONCLUSION:

Prostate cancer is a significant health issue for older men in Australia and New Zealand. New treatment programs capable of improving outcomes for men with prostate cancer may provide significant long term benefits, both to patients and the health system. The high-level data reported by Denham et al (2005) provides considerable evidence for the effectiveness of hormone therapy used prior to and during radiotherapy. It is likely that if there is widespread diffusion, this treatment regimen will replace the current regimen at little additional cost to the health system.

HEALTHPACT ACTION:

It is recommended, therefore, that this summary be disseminated throughout the jurisdictions to inform clinical practice. No further research is required on behalf of HealthPACT.

SOURCES OF FURTHER INFORMATION:

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AIHW (2004). *Cancer in Australia 2001,* Australian Institute of Health and Welfare, Canberra.

AIHW (2005a). *Cancer incident projections Australia 2002 - 2011*, Australian Institute of Health and Welfare, Canberra.

AIHW (2005b). *National Hospital Morbidity Database* [Internet]. Australian Institute of Health and Welfare. Available from: http://www.aihw.gov.au/cognos/cgi-bin/ppdscgi.exe?DC=Q&E=/AHS/principaldiagnosis0304 [Accessed 3rd January 2005].

APCC (2003). *Prostate cancer: a guide for men and their families*, Australian Prostate Cancer Collaboration.

Christie, D., Denham, J. et al (2005). 'Delayed rectal and urinary symptomatology in patients treated for prostate cancer by radiotherapy with or without short term neo-adjuvant androgen deprivation', *Radiother Oncol*, 77 (2), 117-125.

Denham, J. W., Steigler, A. et al (2005). 'Short-term androgen deprivation and radiotherapy for locally advanced prostate cancer: results from the Trans-Tasman Radiation Oncology Group 96.01 randomised controlled trial', *Lancet Oncol*, 6 (11), 841-850.

Laverdiere, J., Gomez, J. L. et al (1997). 'Beneficial effect of combination hormonal therapy administered prior and following external beam radiation therapy in localized prostate cancer', *Int J Radiat Oncol Biol Phys*, 37 (2), 247-252.

NHRMC (2003). *Clinical Practice Guidelines: Evidence-based information and recommendations for the management of localised prostate cancer*, National Health and Medical Research Council, Canberra.

NZHIS (2005). *Cancer: New Registrations and Deaths 2001*, New Zealand Health Information Service, Wellington.

Pilepich, M. V., Winter, K. et al (2001). 'Phase III radiation therapy oncology group (RTOG) trial 86-10 of androgen deprivation adjuvant to definitive radiotherapy in locally advanced carcinoma of the prostate', *Int J Radiat Oncol Biol Phys*, 50 (5), 1243-1252.

TROG (2005). *The 'Radar' Prostate Cancer Trial: Information Package*, Trans Tasman Radiation Oncology Group.

LIST OF STUDIES INCLUDED

Total number of studies	
Level II evidence	2

SEARCH CRITERIA TO BE USED:

Neoadjuvant Therapy
Prostatic Neoplasms/drug therapy/mortality/*radiotherapy
Prostate/pathology