Cancer Council Australia

Clinical practice guidelines for the management of locally advanced and metastatic prostate cancer

Funding received from

1 Management of locally advanced and metastatic prostate cancer

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- In men with advanced prostate cancer, what interventions may ameliorate or minimise the symptoms of fatigue?
- In men with advanced prostate cancer, what is the evidence that specialist palliative care can assist patients and families in providing effective end of life care?

1 Foreword

Foreword

The management of prostate cancer is complex and often confusing for both the patient, his family and the medical and health practitioners involved in his care.

The complexity is due to a range of factors including the biological evolution of prostate cancer, the difficulties arising from the lack of a specific and sensitive non-invasive test that can provide early diagnosis and predict the subsequent progression of the disease. Further, many of the treatment modalities are associated with side effects that can significantly influence the quality of life of the patient. In some instances, the lack of properly controlled clinical trials has resulted in the absence of an evidence base on which to select the best treatment for each patient.

These clinical practice guidelines have been developed following an extensive analysis of papers that can inform the decision making process for the patient, his family and those involved in managing his care. The results of these analyses have been reviewed by the Working Party of the Australian Cancer Network with further support from the Cancer Council Australia. The recommendations encompass the range of treatment modalities and include psycho-social care, complementary and alternatives therapies and the socioeconomic aspects of advanced prostate cancer.

One of the major strengths of this set of recommendations is that it provides the reader with an assessment of the quality of the evidence on which they are based. This enables all concerned in the patient's management to assess the risk-benefit ratios for the range of modalities concerned. The educational value of this document is very high and will assist the decision makers in their difficult decisions. It also sets out the needs of this area of medicine and it challenges all those concerned to continue the search for the best management of the patient and enables the patient to have an involvement in this challenging activity.

I congratulate all involved in this extensive process and hope that the value placed on this document will be some recompense for their work in making this happen.

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2 Preface

2.1 Preface

Attitudes to prostate cancer have changed dramatically over the last 30 years, prior to that time prostate cancer was often considered to require little treatment as it was considered to occur primarily in elderly men and was more often than not metastatic at the time of diagnosis and the only treatment plan often was orchidectomy.

A number of factors have brought about this very significant change in attitude to the management of prostate cancer. The discovery of prostate specific antigen (PSA) coupled with ultra sound guided biopsy of the prostate has meant that prostate cancer is now diagnosed at least a decade or more earlier than was the case in the 1970's and is more likely to be confined to the prostate. The development of nerve sparing techniques and the increased familiarity with radical prostatectomy also the introduction of high dose and more focussed external beam radiation as well as the introduction of brachytherapy have all made local treatment more effective and with reduced morbidity.

However, in spite of these advances a significant proportion of men will still be identified with or develop metastatic disease. This is usually determined now on the basis of a rising PSA after attempts at cure by one of the previously described modalities. However, even in this situation Pound et al 1999[1] data indicated that the median actuarial time for death was 13 years after the initial PSA rise. We cannot cure metastatic disease but given the long life expectancy after the initial PSA rise it is important that men in this situation received the most appropriate treatment to ensure both prolongation of and high quality of life. These guidelines attempt to bring together the best evidence currently available to achieve this goal.

I would like to recognise the work of Professor Dianne O'Connell who has managed the process on behalf of the steering committee and her dedicated small group of researchers who have reviewed the tens of thousands of articles necessary to support this process. Dr Carol Pinnock for developing the consumer guide and Emeritus Professor Tom Reeve AC CBE, whose experience in guideline development and direction has been vital to the success of the project.

I would also like to acknowledge the contribution of the members of the steering committee who have freely given of their time and expertise to bring this project to fruition.

The scope of the exercise turned out to be far greater than we envisaged when we embarked on the project and if it had not been for the generous financial support of Andrology Australia, The Prostate Cancer Foundation of Australia, Cancer Council New South Wales and the Australian Cancer Network we would not have been able to undertake what we believe is the most comprehensive review of the evidence for the management of advanced and metastatic prostate cancer that has been undertaken to date. *(See Appendix – Guideline development process).*

Professor Villis Marshall AC

Chair, Management of Metastatic Prostate Cancer Guidelines Working Party

2.2 References

1. ↑ Pound CR, Partin AW, Eisenberger MA, Chan DW, Pearson JD, Walsh PC. *Natural history of progression after PSA elevation following radical prostatectomy.* JAMA 1999 May 5;281(17):1591-7 Available from: http://www.ncbi.nlm.nih.gov/pubmed/10235151.

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3 Summary of recommendations

3.1 Summary of recommendations

3.2 Psychosocial care

3.2.1 In men with prostate cancer, do interventions improve decision satisfaction, risk comprehension, knowledge about prostate cancer and understanding of their prognosis?

Recommendation	Grade
Men with advanced prostate cancer should be offered education about their cancer, treatment options, and the benefits and disadvantages of available approaches, as well as strategies to manage treatment side effects at each stage in the progression of prostate cancer. A range of formats including written information, verbal instruction and multimedia could be considered.	**C**

3.2.2 In men with prostate cancer, do psychological and cognitive interventions improve psychological adjustment?

Recommendation	Grade
Men with advanced prostate cancer should be offered psychosocial interventions to enhance their adjustment. Effective approaches include group-based cognitive behavioural interventions, nurse delivered education and support, sensory patient education, one-to-one peer support and group education and discussion (support groups). However, psychosocial intervention research for prostate cancer has predominantly been undertaken with men with localised disease. Research addressing the unique psychosocial needs of men with advanced disease is needed.	**B**

3.2.3 In men with prostate cancer, do diet and lifestyle interventions improve quality of life?

Recommendation	Grade
Men with advanced prostate cancer should be advised that resistance exercise and moderate to strenuous physical activity with expert supervision/support can improve quality of life and muscular fitness and reduce fatigue and the impact of fatigue on daily living. Unstable bone lesions and co-morbidities such as cardiovascular disease are exclusion criteria for studies on this topic and so are likely contraindications for this approach.	**D**

3.2.4 In men with prostate cancer, do interventions improve sexual functioning?

Recommendation	Grade
No recommendations are able to be made about effective ways to improve sexual adjustment in men with advanced prostate cancer and their female or male partners. Research into effective interventions for men with advanced prostate cancer is needed.	**D**

3.2.5 In men with prostate cancer, do interventions alleviating partner distress improve quality of life?

Recommendation	Grade
As yet there is insufficient evidence to strongly recommend a specific approach to reducing psychological distress and improving quality of life for the partners of men with advanced prostate cancer. However, group psycho-education may be of benefit. Research into effective interventions for the partners of men with advanced prostate cancer is urgently needed.	**D**

3.2.6 What are the levels of psycho-social distress in men with advanced prostate cancer, including that related to PSA anxiety?

Recommendation	Grade
Health professionals should be aware of risk factors for the development of anxiety and depression and be prepared to treat appropriately.	**B**

3.3 Locally advanced disease

3.3.1 Androgen deprivation therapy (ADT)

3.3.2 What should be done for patients with locally advanced disease who are not suitable candidates for surgery or radiotherapy – primary androgen deprivation at diagnosis or wait until clinical progression (localized or metastatic) - Timing?

Recommendation	Grade
No strong recommendation can be made for the use of androgen deprivation therapy in locally advanced disease. However, there may be a modest benefit for immediate or primary androgen deprivation therapy for patients with locally advanced disease deemed not suitable for definitive local therapy. However, this has to be weighed against the impact of androgen deprivation therapy on quality of life.	**C**

3.3.3 What should be done for patients with locally advanced disease who are not suitable candidates for surgery or radiotherapy – primary androgen deprivation at diagnosis or wait until clinical progression (localized or metastatic)?

Recommendation	Grade
A recommendation cannot be made on the basis of the evidence currently available.	**D**

3.3.4 Are there differences between the different hormone therapy methods in the pattern and severity of toxicity effects for non metastatic disease?

Recommendation	Grade
It is recommended that the prescriber take into account the following points when commencing ADT: ■ The use of non-steroidal anti-androgens as monotherapy may have fewer and less severe adverse events than medical or surgical castration but may still have a toxicity profile that impairs quality of life, and there is little to no efficacy data to support their use as monotherapy. ■ Extrapolating from evidence with metastatic disease (see Overt metastatic disease and/or loco-regional progressive disease), Combined androgen blockade (CAB) with an antiandrogen does increase the adverse event profile versus medical or surgical castration monotherapy and this needs to be weighed up against its marginal additional survival benefits seen in patients with metastatic disease. ■ When the unwanted effects of treatment are preferable to the unwanted effects of the tumour (e.g. prevent recurrence with increased overall survival in adjuvant setting), the side-effect profiles of the treatment options should be explained and strategies to minimise these effects should be considered with the patient.	**B**

3.3.5 What is the incidence of osteoporosis and reduction in bone mineral density at 2, 5 and 10 years and what is the risk of osteoporotic bone fracture due to bilateral orchidectomy (or orchidectomy), LHRH agonist or long term androgen deficiency?

Recommendation	Grade
Before commencing patients on androgen deprivation therapy, consider the likely duration of that treatment and the risk–benefit analysis for the indication for treatment, and take into account the effects on bone mineral density and risks of pathological fractures from osteoporosis.	**C**

3.3.6 What is the effect on Quality of Life as measured by validated questionnaires due to androgen ablation (deprivation or blockade) treatment?

Recommendation	Grade
Toxicities should be considered in the context of what is important to each individual patient, as for some patients impairment of sexual function may have a significant impact on their quality of life and overall adjustment, as well as affecting adversely those close to them.	**C**

3.3.7 Radiotherapy

3.3.8 What is the efficacy of external beam radiotherapy techniques for locally advanced disease?

Recommendation	Grade
When radiation therapy alone is used, limited field radiotherapy has similar efficacy and has less toxicity than whole pelvis and therefore is recommended. The role of whole pelvis radiation is yet to be defined. Consideration should be given to dose escalation (74Gy or higher) if it can be delivered safely.	**C**

Recommendation	Grade
Patients with locally advanced prostate cancer should receive 3D conformal radiation to minimise toxicity.	

3.3.9 What is the efficacy of external beam radiotherapy compared with other treatments for local control for locally advanced disease?

Recommendation	Grade
Based on randomised trial evidence, it is not possible to quantify the degree of benefit provided by radiotherapy alone for locally advanced prostate cancer. The role of surgery or hormonal therapy alone in this group of patients remains to be defined.	**D**
Radiation in addition to hormone therapy improves survival and is recommended.	**B**

3.3.10 What is the efficacy of brachytherapy for locally advanced disease?

Recommendation	Grade
3D conformal dose escalated external beam radiotherapy alone, or reduced dose external beam radiation treatment in combination with high dose-rate brachytherapy, are well recognised radical treatments for locally advanced disease. There is no randomised evidence to suggest superiority or to recommend one modality over the other.	**D**

3.3.11 Radiotherapy and androgen deprivation therapy (ADT)

3.3.12 Is there any survival advantage for androgen blockade (androgen ablation, deprivation) when used as first line therapy in the adjuvant or neoadjuvant setting with radiotherapy for locally advanced prostate cancer?

Recommendation	Grade
It is recommended that patients with locally advanced prostate cancer who are receiving treatment with radical radiotherapy receive long-term androgen deprivation (at least two years).	**B**
Short-term neoadjuvant androgen deprivation therapy can be considered for patients with locally advanced prostate cancer.	**C**
The optimal sequencing and duration of androgen deprivation in relation to radiotherapy is yet to be defined.	**C**

3.3.13 Are cumulative treatment toxicities different when androgen blockade (androgen ablation, deprivation) is used as first line therapy in the adjuvant or neoadjuvant setting with radiotherapy for locally advanced prostate cancer in locally advanced disease?

Recommendation	Grade
Androgen deprivation therapy can be used in combination with radiotherapy without additional radiotherapy toxicities (urinary and gastrointestinal). Effect on sexual functioning has not been defined.	**C**

3.3.14 Surgery

3.3.15 What is the evidence that surgery improves the outcomes in men with locally advanced disease?

Recommendation	Grade
There is insufficient evidence to support the use of surgery in the management of advanced prostate cancer, with the possible exception of a transurethral resection of the prostate in men who are unable to void after androgen deprivation therapy.	**C**

3.3.16 Surgery plus androgen deprivation therapy

3.3.17 For men with locally advanced prostate cancer, is there a role for peri-operative hormone therapy in the following situations: neoadjuvant setting, post-radical prostatectomy short duration, post-radical prostatectomy long duration?

Recommendation	Grade
For locally advanced prostate cancer, anti-androgens as an adjuvant monotherapy to radical prostatectomy are not recommended.	**B**
For node-positive disease androgen deprivation therapy (ADT) should be considered. For patients with fully resected node-positive disease (prostatectomy and lymphadenectomy), it is strongly recommended that patients be counselled on the overall survival benefit of ADT and weighed against the short- and long-term toxicities of androgen deprivation. It is further recommended that patients be counselled on the 'benefit' of improved survival in relation to the 'risk' of therapy – namely the impact of ADT on quality of life.	**C**

3.3.18 Pathologic T3/T4 disease post radical surgery (Patients with extra capsular extension, seminal vesicle involvement or positive surgical margins)

3.3.19 What is the efficacy of radiation post radical prostatectomy in patients with extra capsular extension, seminal vesicle involvement or positive surgical margins for locally advanced disease?

Recommendation	Grade
It is recommended that patients with extracapsular extension, seminal vesicle involvement or positive surgical margins receive post-operative EBRT within four months of surgery. The role of active surveillance and early salvage radiotherapy has not been defined.	**B**

3.3.20 Node-positive disease

3.3.21 Is there any survival advantage for androgen blockade (androgen ablation, deprivation) when used as first line therapy in the adjuvant or neoadjuvant setting with radiotherapy for locally advanced, node-positive prostate cancer?

Recommendation	Grade
If radical radiotherapy is given to patients with node-positive disease it is reasonable to offer long-term androgen deprivation in addition to radiotherapy.	**D**

3.3.22 What is the efficacy of radiation for locally advanced node positive disease?

Recommendation	Grade
There is insufficient evidence to make a recommendation for the use of external beam radiation as alternative or adjuvant to hormone therapies in node-positive patients.	

3.4 Biochemical relapse

3.4.1 What should be done for patients with rising PSA levels and normal testosterone levels following definitive radiotherapy or radical prostatectomy?

Recommendation	Grade
The optimal timing of androgen deprivation therapy in patients with biochemical relapse of disease without evidence of overt metastatic disease is not defined. Eligible patients should be informed about the current TROG Trial comparing early versus delayed hormonal therapy in this group.	

3.5 Overt metastatic disease and/or loco-regional progressive disease

3.5.1 Androgen deprivation therapy

3.5.2 Is any one hormone therapy (androgen ablation) superior to another when given in the first line setting in terms of survival in metastatic disease?

Recommendation	Grade
Patients with metastatic prostate cancer can be treated with either orchidectomy or LHRH agonist based on patient preference. Anti-androgen monotherapy should be avoided as the data indicate this is probably associated with a shorter overall survival.	**C**

3.5.3 Is there any survival advantage for maximum androgen blockade (or combined hormone therapy) compared with single agent androgen blockade when used as first line therapy in metastatic disease?

Recommendation	Grade
Patients with metastatic prostate cancer may be treated with a non-steroidal anti-androgen combined with androgen deprivation therapy as a continuing strategy (beyond the period of LHRH-induced surge [flare] of testosterone) if they are prepared to accept the greater likelihood of unwanted effects from combination therapy. It is recommended that patients with high–volume disease or disease where urgent tumour debulking is required (eg impending spinal canal compression or urinary outflow obstruction) be commenced on combined androgen blockade to prevent flare reactions. This required period is approximately one month for an LHRH agonist and covers the time it takes for testosterone levels to reach a castrate state. Continuation of combined therapy beyond that period may be considered if the patient is prepared to accept the greater likelihood of unwanted side effects from combination therapy.	**B**

3.5.4 For patients with radiologically detectable but asymptomatic disease should hormone therapy be started immediately or should it be started at the onset of symptoms?

Recommendation	Grade
Androgen deprivation therapy is indicated for metastatic prostate cancer. Immediate therapy is warranted for symptomatic metastases. The evidence for immediate therapy for asymptomatic metastases is unclear, but it is definitely warranted if delay may result in complications (eg spinal cord compression from vertebral metastases).	**C**

3.5.5 Are there differences between the different hormone therapy methods in the pattern and severity of toxicity effects in metastatic disease?

Recommendation	Grade
	C

Recommendation	Grade
The benefits of androgen deprivation therapy in controlling a patient's cancer outweigh the ADT adverse-event profile. However, given the clinically relevant and quality-of-life impairing litany of unwanted effects of ADT, the timing of commencement of ADT as a palliative treatment needs to be considered carefully. Assessment of liver function tests, risk of osteoporosis and bone density measurements as required is recommended. Baseline information on what is important to each individual patient should be ascertained (refer Complications and cumulative treatment toxicity). This will permit the commencement and nature of treatment to be tailored and allow an assessment of the cause of adverse effects if they emerge. The common side effects need to be discussed with the patient before commencing any ADT. All patients taking anti-androgens should have their liver function tests monitored.	

3.5.6 What is the effect on Quality of Life as measured by validated questionnaires due to androgen ablation (deprivation or blockade) treatment in metastatic disease?

Recommendation	Grade
Toxicities in the context of what is important to each individual patient should be considered, as decrements in highly valued faculties for some patients may have a significant impact on the quality of life and overall adjustment of those individuals and those close to them.	**C**

3.5.7 Is there a difference in survival for intermittent androgen deprivation compared to continuous androgen deprivation?

Recommendation	Grade
No formal recommendation on intermittent or continuous androgen deprivation therapy can be made based on the lack of definitive data. However, it would appear that there may be a quality of life benefit. Intermittent androgen deprivation therapy can be considered for men who (i) achieve a good remission, (ii) are destined to be on ADT for a prolonged period, and (iii) are having intolerable side effects from long-term androgen deprivation.	**C**

3.5.8 Radiotherapy

3.5.9 What is the effectiveness of local external beam radiotherapy (EBRT) in the palliation of uncomplicated bone pain?

Recommendation	Grade
Radiotherapy is an effective and well-tolerated treatment for metastatic bone pain. A single dose of 8Gy is as effective as higher fractionated doses (eg 20–30Gy) in reducing bone pain. The higher incidence of re-treatment with lower-dose single fraction regimens should be considered as part of the decision-making process.	**C**

3.5.10 What is the evidence for the effect of radiotherapy in palliation of soft tissue disease of EBRT to the prostate for symptom treatment in locally advanced disease and to local metastases (such as the lymph nodes for symptom treatment such as lymphoedema and painful lymph nodes)?

Recommendation	Grade
Radiotherapy can be considered for palliation of symptoms secondary to locally progressive disease.	**D**

3.5.11 What is the benefit of EBRT alone given for malignant spinal cord compression?

Recommendation	Grade
For patients with malignant spinal cord compression the use of radiation is recommended. The optimal fractionation schedule of radiotherapy is unknown.	**D**
Patients being treated with radiation for spinal cord compression should be given dexamethasone at time of diagnosis.	**B**

3.5.12 What is the role of surgery in the treatment of malignant spinal cord compression?

Recommendation	Grade
For highly selected patients with malignant spinal cord compression, vertebrectomy with spinal stabilisation prior to radiotherapy should be considered. The role of decompression laminectomy prior to radiotherapy is unknown.	**C**

3.5.13 What is the efficacy of steroids for the treatment of malignant spinal cord compression?

Recommendation	Grade
Patients being treated with radiotherapy for malignant spinal cord compression should also receive dexamethasone.	**C**
The optimal dose of dexamethasone remains to be defined.	**D**

3.6 Castration-resistant prostate cancer

3.6.1 Androgen deprivation therapy

3.6.2 Is any one hormone therapy (androgen ablation) superior to another when given in the first line setting in terms of survival in metastatic disease?

Recommendation	Grade
There is a sequence of actions that should be followed when a patient is shown to have progressive cancer on androgen deprivation therapy.	**C**

Recommendation	Grade
First, confirm that the patient has a castrate level of testosterone if on an LHRH agonist therapy. If the patient is also on a nonsteroidal anti-androgen, this agent could be withdrawn and observed for the possibility of an anti-androgen withdrawal phenomenon. It is reasonable to trial further hormone manipulations if the patient is asymptomatic or minimally symptomatic prior to use of chemotherapy (e.g. docetaxel).	

3.6.3 Should LHRH agonist be continued when the patient is hormone refractory?

Recommendation	Grade
There is insufficient evidence to make a recommendation as to whether a patient should continue LHRH agonist therapy once his disease has progressed while on androgen deprivation.	**D**

3.6.4 Radioisotopes

3.6.5 What is the effectiveness of unsealed radioisotopes in the management of bone pain from prostate cancer?

Recommendation	Grade
Unsealed radioisotopes may be considered for the management of multifocal bone pain alongside other options of treatment in patients with hormone refractory prostate cancer.	**C**

3.6.6 Do unsealed radioisotopes improve survival in metastatic prostate cancer?

Recommendation	Grade
The impact of unsealed radioisotopes on overall survival in men with castrate-resistant metastatic prostate cancer is undefined. The relative roles of unsealed radioisotopes and the newer chemotherapeutic agents (e.g. taxanes) and bisphosphonates have also not been defined.	**D**

3.6.7 What is the evidence that quality of life is improved with unsealed radioisotopes in prostate cancer?

Recommendation	Grade
It is not known what effect unsealed radioisotopes have on quality of life for men with metastatic prostate cancer.	**C**

3.6.8 What is the toxicity of unsealed radioisotopes for treatment of metastatic prostate cancer?

Recommendation	Grade
Unsealed radioisotopes alone may be associated with higher haematological adverse events compared with supportive care or localised radiation, although overall these rates are low. Unsealed radioisotopes in combination with other treatments such as radiotherapy have higher rates of serious toxicity than radiotherapy alone. The toxicity of unsealed radioisotopes in combination with modern chemotherapy (taxanes) has not yet been defined and caution should be exercised if such combinations are considered.	**C**

3.6.9 Chemotherapy

3.6.10 Does cytotoxic chemotherapy give a survival benefit or any other benefits in terms of quality of life improvement, control of pain or other symptoms compared to patients not receiving chemotherapy or receiving different types of chemotherapy?

Recommendation	Grade
Docetaxel in combination with prednisone is appropriate in the first line setting to improve survival, pain and quality of life in good performance patients with castrate-resistant metastatic prostate cancer.	**B**
The combination of mitoxantrone and prednisolone also offers palliative benefit but no survival benefit compared to docetaxel.	**C**

3.7 Palliative care

3.7.1 In men with advanced prostate cancer, what is the evidence that referral to specialist palliative care can assist in supporting a patient's decision making and treatment planning processes?

Recommendation	Grade
Men with metastatic prostate cancer should be referred for specialist palliative care or a coordinated palliative approach to assist in advance care planning.	**C**

3.7.2 In men with advanced prostate cancer, what is the evidence that referral to specialist palliative care can assist with symptom control?

Recommendation	Grade
Men with metastatic prostate cancer should be referred for interdisciplinary	

Recommendation	Grade
palliative care to assist in symptom control and in providing emotional, social and spiritual support.	**C**

3.7.3 In men with advanced prostate cancer, what is the evidence that specialist palliative care can assist patients and families in providing effective end of life care?

Recommendation	Grade
Men with metastatic prostate cancer and their families should be referred for a coordinated palliative approach to assist in providing effective end-of-life care.	**C**

3.8 Complementary and alternative therapies

3.8.1 Complementary and alternative (unproven) therapies

Recommendation	Grade
Health professionals should ask their patients about their use of CAM therapies in a supportive, understanding and non-judgmental way.	**D**
Calcitriol in combination with docetaxel chemotherapy is not recommended on the basis of a large randomised trial which found excess mortality.	**A**
Lycopene may benefit a small group of men with metastatic prostate cancer who have had no radiotherapy, no hormone therapy and who have had orchidectomy. In view of these findings, lycopene deserves to be further trialled.	**C**
There is insufficient evidence to make any recommendations on dietary	

Recommendation	Grade
supplements in relation to quality of life, pain relief and toxicity.	**C**

3.9 Socio-economic aspects of advanced prostate cancer

3.9.1 Socio-economic aspects of advanced prostate cancer

Recommendation	Grade
Based on a lack of evidence from randomised trials or observational studies, it is not possible to determine whether socio-economic status is associated with differences in outcomes for men with locally advanced or metastatic prostate cancer.	**D**

4 Introduction

Contents

4.1 Introduction to prostate cancer

4.1.1 Natural history and staging of prostate cancer

Prostate cancer has many uncertainties associated with its management. A major problem for any review at present arises from the difficulty in establishing with certainty that the cancer is confined to the prostate at the time of diagnosis.

Currently, through a combination of PSA measurement and ultra-sound-guided biopsy, it is now possible to establish with greater certainty than before the local extent of the cancer within the gland and its likely aggressiveness by application of the Gleason scoring system. This information, when incorporated with other measurable factors into nomograms, has enabled clinicians to establish the probability but not the certainty of the cancer being confined to the prostate.

Before the introduction of PSA it was easier to be certain that a person had metastatic disease on the basis of a positive bone scan or computed tomography (CT). Unfortunately, while the bone scan has a high level of specificity its sensitivity is too low and in current prostate cancer management, bone scans have little use in determining the presence of metastatic disease. Consequently, after presumed curative treatment for local disease, a rising PSA is now used as a surrogate marker for metastatic disease. There is urgent need for a more sensitive and specific test to predict the metastatic potential of an individual cancer.

This review initially intended to focus on metastatic disease, but for the reasons outlined above the scope was expanded to include locally advanced as well as metastatic cancer. It is acknowledged that it is often difficult to establish from published articles whether the disease was locally advanced or metastatic because of the ‘grey zone’ resulting from the imprecision of our current staging modalities. Locally-advanced disease for the purpose of the review has been defined as T3/T4 and/or early-stage disease with PSA greater than 20.

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4.1.2 Prostate cancer in Australia

The Australian Institute of Health and Welfare (2008) report[1] based on 2005 data predicted that the risk of a male being diagnosed with cancer before age 75 was one in three and before age 85 was one in two. Given that 29% of male cancers arise from the prostate, and assuming a relatively constant pattern of the incidence of cancers as men age, prostate cancer is likely to continue to be a major male health issue as our population ages. We know that approximately 3000 men die each year from prostate cancer[2] and while earlier diagnosis and more aggressive local therapy have been available for at least a decade, the death rate has not declined greatly. The age-standardised mortality rate in 1999 was 35 deaths per 100,000 males and in 2005 was 32.8 deaths per 100,000 males. It is also worthy of note that 84% of deaths from prostate cancer in 2003 occurred in men over the age of seventy.

It is therefore evident that for the foreseeable future we will continue to need to care for a significant number of older men with metastatic disease. A cure for metastatic cancer would be the ideal but seems unlikely in the short term. The middle ground is to try to ensure the information currently available is used appropriately to achieve optimal cancer control for these men while preserving the best quality of life. The development of these guidelines is one step in trying to achieve this goal.

As part of the original plan no systematic review of evidence took place after (April) 2006. We recognised that this is a limitation of the guidelines. We also recognised that there will need to be a prolonged period of consultation as part of the process of acceptance of guidelines by the NHMRC and this will add to the time between the end of the review and the final publication of the guidelines. To try to in part to address this issue, we noted and provided references for high quality randomised controlled trials where the review team believed that this more contemporary information may cause clinicians to reflect on the interpretation and relevance of the recommendations, given that the recommendations were all based on the systematic review of the evidence available as of April 2006. Another important consideration is the significant change in the way medicine is practised, with a much greater focus on informed and shared decision making. The development of these guidelines has provided the evidence base for the production of a consumer guide that will facilitate shared decision making as men and their families confront the health issues associated with the management of advanced and metastatic prostate cancer.

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5 Psychosocial care

5.1 Psychosocial care

The diagnosis and subsequent treatment of cancer is a major life stress that is followed by a range of well-described psychological, social, physical and spiritual difficulties. Men with advanced prostate cancer where curative intent is no longer the treatment goal, face distinct challenges compared with men with localised prostate cancer. As outlined in these guidelines, the iatrogenic effects of hormonal ablation include mood disturbance, cognitive impairment, hot flushes, osteoporosis, fatigue, sexual dysfunction, and changes in muscle mass and adiposity. Men with advanced prostate cancer face the dilemma of choosing not only a specific treatment, but also the timing of treatment initiation and the difficult task of weighing up the pros and cons of various approaches.[1] Decision support is particularly salient given most men with prostate cancer

prefer active involvement in decision making about treatment.[2][3][4][5] Further, in comparison to men with localised prostate cancer, men with advanced disease report higher levels of psychological distress, poorer quality of life and greater unmet supportive care needs.[6][7][8] As well, partners of men with prostate cancer report high levels of psychological distress than are experienced by the men themselves.[9] Hence, guidance is crucial for men with advanced prostate cancer and their families on steps to maximise quality of life and to enhance and protect interpersonal relationships.

Peer support through the Prostate Cancer Foundation of Australia and state-based Cancer Councils is currently broadly available. In a large Australian cross-sectional survey of group members, this type of support was positively endorsed by men as a helpful source of emotional and informational support.[7] This is mirrored in similar studies elsewhere.[10]However, to date there are significant limitations in research into the psychosocial aspects of prostate cancer. Limitations include the use of small convenience samples, cross-sectional designs, limited follow up, and a general failure to adhere to CONSORT (CONsolidated Standards of Reporting Trials) guidelines.[11][12] In the case of advanced prostate cancer there is scant intervention research that specifically targets the concerns and needs of these men and their families. As a result, the scope of this review was by necessity extended to studies of men with localised or mixed-stage disease, and their partners where possible. There is an urgent need for research, health policy and planning to focus efforts and attention specifically on men with advanced prostate cancer and their families.

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Clinical questions:

- In men with prostate cancer, do interventions improve decision satisfaction, risk comprehension, knowle about prostate cancer and understanding of their prognosis?
- In men with prostate cancer, do psychological and cognitive interventions improve psychological adjustm
- In men with prostate cancer, do diet and lifestyle interventions improve quality of life?
- In men with prostate cancer, do interventions improve sexual functioning?
- In men with prostate cancer, do interventions alleviating partner distress improve quality of life?

Questions, for which no systematic review undertaken and were dealt with descriptively:

- What are the levels of psycho-social distress in men with advanced prostate cancer, including that relate PSA anxiety?
- What are the unmet supportive care needs of men with advanced prostate cancer? - with particular focu Australian men -> see above introduction

Questions, for which no relevant evidence was found during the systematic review:

- What is the evidence that multidisciplinary care for men with locally advanced or metastatic prostate car is effective?
- Are there interventions that promote hope, meaning making, satisfaction with life and positive adjustme

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5.3 Appendices

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5.1 Introduction

5.1.1 Psychosocial care

The diagnosis and subsequent treatment of cancer is a major life stress that is followed by a range of well-described psychological, social, physical and spiritual difficulties. Men with advanced prostate cancer where curative intent is no longer the treatment goal, face distinct challenges compared with men with localised prostate cancer. As outlined in these guidelines, the iatrogenic effects of hormonal ablation include mood disturbance, cognitive impairment, hot flushes, osteoporosis, fatigue, sexual dysfunction, and changes in muscle mass and adiposity. Men with advanced prostate cancer face the dilemma of choosing not only a specific treatment, but also the timing of treatment initiation and the difficult task of weighing up the pros and cons of various approaches.[1] Decision support is particularly salient given most men with prostate cancer prefer active involvement in decision making about treatment.[2][3][4][5] Further, in comparison to men with localised prostate cancer, men with advanced disease report higher levels of psychological distress, poorer quality of life and greater unmet supportive care needs.[6][7][8] As well, partners of men with prostate cancer report high levels of psychological distress than are experienced by the men themselves.[9] Hence, guidance is crucial for men with advanced prostate cancer and their families on steps to maximise quality of life and to enhance and protect interpersonal relationships.

Peer support through the Prostate Cancer Foundation of Australia and state-based Cancer Councils is currently broadly available. In a large Australian cross-sectional survey of group members, this type of support was positively endorsed by men as a helpful source of emotional and informational support.[7] This is mirrored in similar studies elsewhere.[10]However, to date there are significant limitations in research into the psychosocial aspects of prostate cancer. Limitations include the use of small convenience samples, cross-sectional designs, limited follow up, and a general failure to adhere to CONSORT (CONsolidated Standards of Reporting Trials) guidelines.[11][12] In the case of advanced prostate cancer there is scant intervention research that specifically targets the concerns and needs of these men and their families. As a result, the scope of this review was by necessity extended to studies of men with localised or mixed-stage disease, and their partners where possible. There is an urgent need for research, health policy and planning to focus efforts and attention specifically on men with advanced prostate cancer and their families.

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5.2 Psychosocial interventions

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5.2.1 In men with prostate cancer, do interventions improve decision satisfaction, risk comprehension, knowledge about prostate cancer and understanding of their prognosis?

No studies specifically addressed this matter for men with known advanced prostate cancer. No studies were identified that assessed the effect of interventions on men's risk comprehension, decision satisfaction, and understanding of their prognosis. Six randomised controlled trials and one case series have assessed the impact of intervention mainly on men's knowledge and desire for involvement in decision making. One of these studies was of medium quality and the others were of low quality.

Davison and Degner[1] undertook a low-quality randomised controlled trial with 60 men newly diagnosed with prostate cancer, comparing written information augmented by an audiotape of medical consultation to written information alone. Stage of disease was not described, however most men were being treated with radical prostatectomy so these were probably men with localised disease. At the six weeks post-test assessment, men who received the augmented information took a more active role in treatment decision-making compared with men who received only written information. In the group that received the audiotape, an additional 40% of men (95% CI: 18–62%, p<0.0001) took an active role at the post-test assessment.

Lepore and Helgeson[2] undertook a low-quality randomised controlled trial with 24 men who had recently completed treatment for localised prostate cancer. The study compared six-weekly lectures plus peer discussion versus a control group. Two weeks after the intervention, men in the interventiongroup experienced greater improvements in knowledge in comparison to controls (p<0.001). In a subsequent study, Lepore et al[3] assessed the effectiveness of group education versus group education plus peer discussion versus control in a randomised controlled trial with 250 men with mixed-stage prostate cancer. This study was of medium quality. Two weeks after the intervention, men who received group education or group education plus peer discussion experienced significantly greater improvements in knowledge compared with controls (p<0.01).

Templeton et al[4] undertook a randomised controlled trial of an evidence-based education package supplemented with verbal teaching by a urology nurse with 55 men on hormonal manipulation. The study was of low quality and stage of disease was not assessed. Men who received the education package experienced greater improvements in knowledge and satisfaction with care in comparison to controls at one month post-intervention. The mean changes from pre- to post-test were larger in the groups receiving the education package by 6.22 (out of 14) 95% CI: 4.80 to 7.64 (p<0.0001) for disease knowledge, 4.31 (out of 10) 95% CI: 3.20 to 5.42 (p<0.001) for treatment knowledge and 3.29 (out of 32) 95% CI: 1.72 to 4.86 (p=0.0001) for satisfaction.

Flynn[5] recruited 67 newly-diagnosed men in a case series to assess the effectiveness of multimedia education about prostate cancer and found significant improvements in overall knowledge immediately after receiving the education program (knowledge change =1.76 95% CI: 0.98 to 2.54, p<0.001). This included improvements in knowledge about cancer in general and prostate anatomy (change= 0.33, 95% CI: 0.005 to 0.61, p<0.05); disease advancement (change= 0.38 95% CI 0.12 to 0.64, p<0.01); aims and side effects of radiotherapy

(change= 0.28 95% CI: 0.03 to 0.53, p<0.05), and hormone therapy (change 0.63 95% CI: 0.35 to 0.91, p<0.001). This study was of low quality. In summary, consistent improvements in men's knowledge about prostate cancer have been achieved from a range of approaches that include written information, nurse instruction, multimedia and group education and peer discussion. The clinical impact of knowledge is unclear. However, knowledge about treatment options and effects is considered necessary for informed consent, shared decisionmaking, compliance with treatments, and self care.

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5.2.2 Evidence summary and recommendations

Evidence summary	Level	References
There is good evidence that men's knowledge of prostate cancer and its treatment can be improved by educational interventions delivered through a range of methods including written and multimedia information, verbal instruction, group education and peer discussion. In addition, involvement in decision-making can be increased through the use of written information and an audiotape of the medical consultation.	II, IV	[1], [2], [3], [4], [5], [6], [7]

Evidence-based recommendation	Grade
Men with advanced prostate cancer should be offered education about their cancer, treatment options, and the benefits and disadvantages of available approaches, as well as strategies to manage treatment side effects at each stage in the progression of prostate cancer. A range of formats including written information, verbal instruction and multimedia could be considered.	**C**

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5.3 Effect of psychosocial interventions on psychological adjustment

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5.3.1 In men with prostate cancer, do psychological and cognitive interventions improve psychological adjustment?

No studies specifically addressed this question for men with advanced prostate cancer, although one low-quality study recruited men on hormonal manipulation but did not assess disease stage.[1] Only one medium-quality study was identified.[2] While it is reasonable to assume the general approaches utilised in studies with men with localised disease are likely to be acceptable to men with metastatic disease, the problems faced by these two groups of men differ. For example, the side-effect profile of radical prostatectomy differs markedly to that of

hormonal ablation; and men who have incurable disease face a different psychological challenge to men receiving treatment with curative intent, as indeed do their spouses. However, while caution should be applied in generalising the outcomes of these studies to men with metastatic prostate cancer, the beneficial effects and clinical importance of psychosocial intervention for all cancer patients and their families is now well established through clinical practice guidelines both in Australia and North America.[3] [4]

Studies differed in the type of intervention, patient group and outcome measured, nevertheless, four low quality studies were identified that utilised a primarily educational approach to intervention, and of these three investigated men receiving radiation therapy for localised prostate cancer. Johnson et al[5] undertook a randomised controlled trial assessing the effectiveness of an education audiotape about radiation therapy with 84 men scheduled to receive this treatment for localised prostate cancer. Compared with men who received general social contact from research staff, over the course of treatment men who received the audiotape experienced less disruption in recreation and pastime activities ($p<0.02$), but no differences were found for mood. In a subsequent study Johnson[6] recruited 62 men who were undergoing radiation therapy for prostate cancer and randomised them to one of three different types of audio-taped messages: (i) coping and self-care advice; (ii) treatment-focussed patient education or (iii) non-focussed information (control group). For mood, men who were low in optimism benefited most from treatment-focussed patient education ($p<0.05$).

Kim et al[7] randomised 152 men receiving radiation therapy for localised prostate cancer to a sensory informational instruction audiotape versus general self-care instruction audiotapes. The sensory informational tape included descriptions of the physical environment during treatment such as sounds heard, the specific side effects expected and when they were most likely to occur. After their last radiotherapy treatment, men who received the sensory informational audiotape reported less fatigue ($p<0.06$) and better sleep ($p<0.03$) than men who received general self-care instruction. No differences were observed for mood. In contrast to the three previous studies, Templeton et al[1] recruited 55 men on hormonal manipulation in a randomised controlled trial of an evidence-based education package supplemented with verbal teaching by a urology nurse. Men who received the education package experienced greater improvements in quality of life by comparison to controls at one month post-intervention. It was not possible to ascertain the size of the effect from the data presented.

Lepore and Helgeson[8] utilised a broader intervention approach that combined education with peer support in a low-quality randomised controlled trial with 24 men who had recently completed treatment for localised prostate cancer. The study compared six weekly lectures plus peer discussion jointly facilitated by a nurse and psychologist versus a control group. Two weeks after the intervention, men in the intervention group experienced greater improvements in mental health subscale of the mental functioning domain of the SF36 ($p<0.05$); less distress about cancer-related thoughts ($p<0.05$); less conflict with their partners ($p<0.01$) and family/friends ($p<0.05$); and greater self-efficacy ($p<0.05$). In a subsequent larger study of medium quality, Lepore et al[2] and Helgeson et al[9] assessed the effectiveness of group education versus group education plus peer discussion versus control in a randomised controlled trial with 250 men with mixed-stage prostate cancer. In the twelve month follow-up period men who received group education plus peer discussion were more likely to maintain steady employment ($p<0.05$) compared with the other conditions; and experienced less sexual bother compared with controls. Men with less education, lower self esteem, lower prostate self efficacy, and higher depressive symptoms benefited most.

Scura et al[10] randomised 17 men newly diagnosed with prostate cancer to nurse-delivered telephone support over a 12-month period supplemented with written materials versus written material only. The study was low quality and no significant effects were found. Qualitative data from participants suggested that telephone nurse support was acceptable to these men.

Penedo et al[11]undertook a low-quality study where 92 men treated previously for localised prostate cancer were randomised to either a ten-week group-based cognitive behavioural intervention or a halfday educational seminar. Men who received the ten-week intervention reported post-intervention improvements in quality of life (Functional Assessment of Cancer Therapy–General Module or FACT-G) ($p<0.03$). In a subsequent study, Penedo et al[12] repeated this trial design with 191 men treated previously for localised prostate cancer. This study was also of low quality. Men who received the cognitive behavioural intervention reported post-intervention improvements in benefit finding ($p<0.01$) and quality of life ($p<0.01$). No improvements were observed for men who attended the halfday seminar. Effect sizes were small.

Giesler et a[13] randomised 99 men newly diagnosed with prostate cancer along with their partners to receive a nurse-driven computer-assisted intervention or standard care. The intervention focussed on symptom management and psycho-education and was tailored to men who had received treatment for localised disease. Men were followed for twelve months. At that time men in the intervention group reported less cancer worry ($p<0.03$) and fewer sexual limitations ($p<0.02$) compared with men who received standard care.

By contrast, peer support for people with cancer is seldom evaluated in gold-standard intervention designs. This may be due in part to this source of support emerging from a community lay setting rather than as a professionally driven care model. Poole at al[14] in a low-quality study compared 142 men in prostate support groups to 92 non-attenders and found no difference in quality of life between the two groups of men. Steginga et al[15] undertook a survey of 1224 men previously treated for prostate cancer who were members of prostate cancer support groups affiliated with the Prostate Cancer Foundation of Australia. This level IV study found high levels of satisfaction with the support provided by these groups, with no differences in satisfaction between professionally- or peer-led groups. The strongest predictor of satisfaction with support was the man’s perception that his clinician was supportive of the group ($p<0.01$). Men with more pain ($p=0.01$), a poorer quality of life and higher distress ($p<0.01$) were less positive in their endorsement of the groups. In the one peer-support study identified that utilised a randomised controlled design, Weber et al[16] recruited 30 men who had received a radical prostatectomy to compare a series of eight weekly meetings with a supportive peer with usual care. Peers were long-term survivors of prostate cancer who had also been treated with radical prostatectomy. At four weeks, men in the intervention group reported less depression ($p<0.02$). However this effect was not evident at eight weeks. At eight weeks men who received the peer support reported less sexual bother ($p=0.01$).

In summary, research into psychosocial interventions for men with prostate cancer is still developing.Despite this, there is good evidence that such care produces a range of positive outcomes for men and work elsewhere underscores the importance of psychosocial support being included in care pathways.[3] [4] It can be argued that men with advanced disease carry a higher individual disease burden than do men with localised disease. The lack of research activity targeting these men’s needs should be addressed by non-government and government cancer control agencies as a priority.

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5.3.2 Evidence summary and recommendations

Evidence summary	Level	References
There is good evidence that a range of intervention approaches have positive effects on adjustment outcomes such as quality of life, benefit finding, cancer worry, sleep, fatigue, sexual bother, work role, recreational activities, health behaviours and physical functioning. Men who are more depressed, have lower levels of education, have lower self esteem and self-efficacy may benefit more from intervention. Effective approaches include group-based cognitive behavioural interventions, nurse-delivered education and support, sensory patient education, one-to-one peer support and group education with peer discussion. Most studies are on men with localised disease.	II	[1], [2], [5], [6], [7], [8], [10], [11], [13], [14], [16], [17]

Evidence-based recommendation	Grade
Men with advanced prostate cancer should be offered psychosocial interventions to enhance their adjustment. Effective approaches include group-based cognitive behavioural interventions, nurse delivered education and support, sensory patient education, one-to-one peer support and group education and discussion (support groups). However, psychosocial intervention research for prostate cancer has predominantly been undertaken with men with localised disease. Research addressing the unique psychosocial needs of men with advanced disease is needed.	**B**

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5.3.3 References

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5.3.4 Appendices

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5.4 Effect of diet and lifestyle interventions

Contents

5.4.1 In men with prostate cancer, do diet and lifestyle interventions improve quality of life?

No randomised controlled trials assessed the effects of dietary interventions on quality of life. Several studies investigated the effects of such interventions on clinical indicators of disease progression and these are covered in Chapter 8 Complementary and alternative therapies in these guidelines. Five low-quality studies and one high-quality study assessed the effects of physical activity interventions on symptom side effects and quality of life.

Culos-Reed[1] in a small uncontrolled study (n=31) showed that a 12-week theory-based physical activity intervention in men receiving hormone therapy for at least six months could increase strenuous physical activity ($p<0.01$) and fitness levels ($p<0.01$) in participants. However, the post-test effects on quality of life were less clear. A non-significant increase occurred in global quality of life and a reduction in fatigue was marginally significant ($p=0.05$).

Carmack-Taylor[2] undertook a low-quality randomised controlled trial with 134 men with prostate cancer receiving continuous androgen ablation to compare a lifestyle group with general psychoeducation. The study had three arms: a group-based lifestyle program where participants were taught cognitive-behavioural skills to enhance self-efficacy in maintaining an active lifestyle versus a groupbased educational support program versus a control group. No significant differences in physical activity levels, body composition or quality of life were found between the three groups of men over a 12-month period despite good adherence to both intervention arms.

Berglund[3] showed no difference in quality of life outcomes in a low-quality randomised trial of a seven-week physical activity (movement and fitness training) program compared with standard care, an information-only or combined physical exercise–information program. The study involved 211 men newly diagnosed with prostate cancer at various stages. The investigators found that stage (presence or absence of metastases) was a stronger predictor of quality-of-life status than intervention group.

Segal[4] undertook a low-quality randomised controlled trial comparing the effects of a resistance exercise program (training three times per week for 12 weeks) on muscular fitness, body composition, fatigue and quality of life (FACT-P) in 155 men receiving androgen therapy for at least three months. While body composition did not change, muscular fitness did increase, accompanied by a 2.2-point reduction in fatigue score (p=0.002 for difference between groups). The FACT-P quality-of-life score also increased by 2.0 points (p=0.001 for difference between groups). The intervention was effective in men receiving androgen deprivation therapy (ADT) for both curative and palliative intents, and receiving ADT for less than or more than one year.

The effectiveness of resistance training in improving muscle strength, endurance and other fitness parameters was also shown by Galvao[5]; however this case series of ten men did not include qualityof-life or symptom outcomes. These authors suggested that for men receiving androgen ablation, resistance training improves muscle endurance and functional capacity that then enhances their ability to carry out activities of daily living with less fatigue.

Windsor et al[6] undertook a high-quality randomised controlled trial with 66 men of the effect of a home-based moderate-intensity (30 minutes, three times per week) walking program on fatigue and walking fitness amongst men undergoing radiotherapy for mixed-stage (majority T1, T2) prostate cancer. Fatigue increased in the control group (p=0.01), but not in the intervention group (p=0.20). However the difference between groups was not statistically significant. The shuttle-test distance (walking fitness) increased in the intervention group by 67 meters (p=0.0003), but not in the control group (p=0.49), with a statistically significant difference between groups at four weeks (difference in means = 111.5 95% CI: 40.5 to 182.5, p=0.003). Generic quality-of-life measures were not included.

In summary, physical activity interventions, both cardiovascular and strength-based, which increase fitness have been shown to reduce fatigue after radiotherapy and fatigue associated with androgen ablation. Generic quality of life has also been shown to improve for men receiving androgen ablation. The effect of physical activity programs on symptoms other than fatigue, and on fatigue in other treatment contexts such as chemotherapy, has not yet been demonstrated.

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5.4.2 Evidence summary and recommendations

Evidence summary	Level	References
There is good evidence that resistance exercise and moderate to strenuous physical activity improves quality of life and muscular fitness and reduces fatigue and the impact of fatigue on daily living for men with prostate cancer.	II	[2], [4], [6]

Evidence summary	Level	References
There are few studies in the area and further research is needed where stages of disease and treatment approaches are controlled and acceptability and compliance with exercise protocols are assessed in order to develop guidelines on optimal exercise levels and patient suitability.		

Evidence-based recommendation	Grade
Men with advanced prostate cancer should be advised that resistance exercise and moderate to strenuous physical activity with expert supervision/support can improve quality of life and muscular fitness and reduce fatigue and the impact of fatigue on daily living. Unstable bone lesions and co-morbidities such as cardiovascular disease are exclusion criteria for studies on this topic and so are likely contraindications for this approach.	**D**

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5.4.3 References

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5.5 Effect of sexual functioning interventions

Contents

5.5.1 In men with prostate cancer, do interventions improve sexual functioning?

No studies specifically addressed this question for men with locally advanced, advanced or metastatic prostate cancer. Neither have ways to help homosexual men and their partners cope sexually after prostate cancer been addressed, which is a further gap in the evidence. One low-quality study of men with localised disease was identified.

Canada et al[1] recruited 84 couples to a randomised controlled trial comparing a couple's focussed intervention with a patient-only intervention. Patients were men who were survivors of localised prostate cancer previously treated with surgery or radiotherapy. The intervention included sexual education, behavioural homework, sexual communication and stimulation skills. Partner participation did not improve outcomes. Only 61% of participants completed the intervention. This could reflect reduced feasibility, acceptability or efficacy of the intervention. At three months post-intervention, patients who had completed the intervention (counselling) had less overall distress ($p<0.01$), better global sexual function ($p<0.0001$) and partners had better global sexual function ($p<0.05$). A falling off in female sexual function was noted at six months although utilisation of erectile dysfunction aids increased ($p<0.003$).

In summary, research to date is uninformative about how to assist men with advanced prostate cancer and their intimate partners, male or female, in managing the sexual side effects of treatment.

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5.5.2 Evidence summary and recommendations

Evidence summary	Level	References
No studies were identified that aimed to improve sexual functioning in men with advanced prostate cancer and their partners. One low quality study that specifically targeted sexual functioning in men with localised disease was identified. However, as the effects of hormone therapy are clinically different to those associated with treatment with curative intent, these are not relevant to men with advanced prostate cancer.	II	[1], [2]

Evidence-based recommendation	Grade
No recommendations are able to be made about effective ways to improve sexual adjustment in men with advanced prostate cancer and their female or male partners. Research into effective interventions for men with advanced prostate cancer is needed.	**D**

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5.5.3 References

1. ↑ [1.0] [1.1] Canada AL, Neese LE, Sui D, Schover LR. *Pilot intervention to enhance sexual rehabilitation for couples after treatment for localized prostate carcinoma.* Cancer 2005 Dec 15;104(12):2689-700 Available from: http://www.ncbi.nlm.nih.gov/pubmed/16294343.
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5.6 Effect of interventions to alleviate partner distress

Contents

5.6.1 In men with prostate cancer, do interventions alleviating partner distress improve quality of life?

No studies specifically addressed this question for men with advanced prostate cancer. Two low quality studies with the female partners of men with localised or mixed-stage disease were identified.[1] [2]

Manne et al[2] randomly assigned 60 wives of men with prostate cancer to either a psycho-education group or no treatment, and assessed a range of adjustment outcomes. Most of the women had husbands with stage II prostate cancer (68%). One month after completion of the group, by comparison to controls, women in the intervention group had less denial ($p<0.01$), more posttraumatic growth (significant subscore differences with p values ranging from 0.02 to 0.04) and reported gains in positive-reappraisal coping ($p=0.05$). No effect was found for distress. This study was of low quality.

In a more recent study, Campbell et al[3] randomised 40 African American prostate cancer survivors (from 157 eligible patients) and their intimate partners to six sessions of tele-based cognitive behavioural therapy or standard care. Men in the intervention group reported significant improvements in bother caused by bowel problems ($p=0.04$) compared with controls; adjustment outcomes for partners in the intervention arm did not differ significantly from partners in standard care. This study was of low quality.

In summary, research to date does not clearly identify the best way to reduce partner distress.

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5.6.2 Evidence summary and recommendations

Evidence summary	Level	References
	II	[1], [2]

Evidence summary	Level	References
No moderate- or high-quality studies addressed the outcome. However in one study, group psycho-education led to short-term improvements in female spouse post-traumatic growth and more use of positive-reappraisal coping and less denial. Studies to investigate ways to promote adjustment and quality of life for the partners of gay men with prostate cancer have not been described.		

Evidence-based recommendation	Grade
As yet there is insufficient evidence to strongly recommend a specific approach to reducing psychological distress and improving quality of life for the partners of men with advanced prostate cancer. However, group psycho-education may be of benefit. Research into effective interventions for the partners of men with advanced prostate cancer is urgently needed.	**D**

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5.6.3 References

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3. ↑ Campbell LC, Keefe FJ, Scipio C, McKee DC, Edwards CL, Herman SH, et al. *Facilitating research participation and improving quality of life for African American prostate cancer survivors and their intimate partners. A pilot study of telephone-based coping skills training.* Cancer 2007 Jan 15;109(2 Suppl):414-24 Available from: http://www.ncbi.nlm.nih.gov/pubmed/17173280.

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5.6.4 Appendices

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5.7 Depression and anxiety

Contents

5.7.1 What are the levels of psycho-social distress in men with advanced prostate cancer, including that related to PSA anxiety?

Up to 35% of patients with cancer experience clinically significant distress,[1] with this rate increasing even further when the person has poor prognosis and experiences more symptom burden. Research into anxiety and depression in men with prostate cancer lags behind comparable research in women with breast cancer, and there is limited evidence to guide specific recommendations in this population. An Australian cross-sectional study of 195 men diagnosed with prostate cancer between 7 and 71 months previously reported that 12% of the sample had clinically significant levels of anxiety, and 16% had similar levels of depression.[2] None of the subjects in this study had advanced disease. A cross-sectional study of 716 men with prostate cancer aged 50-93 years evaluated depression using the Hospital Anxiety and Depression Scale. This study found that aging was related to less distress and less anxiety, but greater depressive symptoms.[3]

Research in patients with advanced prostate cancer is similarly limited. A prospective study conducted in the US examined depression and fatigue in 53 men with recurrent or advanced prostate cancer who had been randomised to treatment with either parenteral leuprolide or oral bicalutamide.[4] Over a 12 month period rates of at least mild depression ranged from 10.4% to 16.3%, with no significant differences between the groups, and no significant change in depression over time, despite the fact that fatigue increased during this period.

The following studies relate to mixed cancer populations with advanced disease. One study of 33 males and 35 females with advanced cancer reported prevalence of anxiety and depression as 25% and 22% respectively.[5] Although structured measures of mood were used, the response rate was low, and only 13% of the subjects had prostate cancer. A cross-sectional study of 74 patients attending a palliative care day unit found that depression affected one in four patients.[6] Pain and low mood were noted to be closely related, although the direction of causality is not clear. The proportion of patients with prostate cancer in the sample was not stated, although the male/female ratio was equal and all patients had advanced disease.

Detection and treatment of anxiety and depression is important for several reasons. Analysis of studies involving 16,922 patients with chronic medical illness demonstrated that patients with depression had significantly greater symptoms when severity of medical illness was controlled for.[7] Furthermore, depression

has been reported to be associated with reduced adherence to recommended treatments amongst patients with medical illness.[8]The identification of depression is aided by attention to known risk factors for psychological morbidity. These include advanced stage of disease; presence of pain or functional disability; side-effects of treatment; fatigue and poor prognosis.[9] Individual risk factors include a past history of depression, economic adversity, lack of social support and poor marital or family functioning.[9] Treatment of anxiety and depression is generally effective and ideally incorporates psychotherapeutic interventions and often the use of medications. [9] However, an Australian randomised controlled trial of antidepressant medication in patients with advanced cancer demonstrated no survival advantage and no benefit for mood for patients who did not meet criteria for major depressive disorder.

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5.7.2 Evidence summary and recommendations

Evidence summary	Level	References
There is little high-quality evidence describing the prevalence of anxiety and depression in patients with advanced prostate cancer.	III-3	[5], [6], [8]

Evidence-based recommendation	Grade
Evidence from research in mixed cancer populations is that anxiety and depression are important comorbidities experienced by patients with advanced cancer, and that effective treatments are available.	**B**

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5.7.3 References

1. ↑ Zabora J, BrintzenhofeSzoc K, Curbow B, Hooker C, Piantadosi S. *The prevalence of psychological distress by cancer site.* Psychooncology 2001;10(1):19-28 Available from: http://www.ncbi.nlm.nih.gov/pubmed/11180574.
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5.7.4 Appendices

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6 Locally advanced disease

6.1 Locally advanced disease

(Locally advanced/high-risk prostate cancer—de novo presentation (clinical stage T3–4, and/or early-stage disease with PSA>20)

6.1.1 Introduction

In these guidelines locally advanced/high risk prostate cancer is usually defined by clinical stage T3-4 and or early stage disease with PSA>20. However, to establish with certainty that it is locally advanced can be difficult and apart from clinical staging and the level of PSA, MRI scans can sometimes be of assistance as well as CT pelvis but both have low sensitivity. The presence of positive margins in the surgically resected specimen also points to the potential for locally advanced disease as does an early rise in the PSA, the rate of rise prior to localised treatment has also been suggested as a potential indicator of metastatic disease. However, in most cases it is the persistent rise in the PSA that has become a surrogate marker for advanced or metastatic disease after surgical resection of the prostate. Post radiotherapy if the PSA reaches its nadir and then starts to rise this

is usually used as a surrogate marker of advanced disease. A measurable PSA after radical prostatectomy does not always indicate residual disease, as it could be due rarely to residual benign tissue. Biopsy of the prostatic bed can be performed to try to obtain tissue and /or monitoring of the rate of rise of the PSA in conjunction with knowledge of the Gleason score and presence of positive or negative margins may provide a means of determining whether the rise is due to a small remnant of benign tissue rather than metastatic disease.

Androgen Deprivation can be achieved in a number of ways. Testicular androgen production can be prevented by surgical castration, by chemical castration through the use of LHRH agonists, or by suppression of androgen production by oestrogens although because of undesirable cardiac side effects oral oestrogens are now rarely used. The other strategy is to use steroidal and non steroidal anti-androgens that compete with both testicular and andrenal androgens for the androgen receptor binding sites. These agents can be used singly and or in combination. It is important to note that there are some restrictions regarding the prescribing of these agents. LHRH agonists are available on the RPBS and anti androgens are only available on the PBS (authority) in combination with ADT. The non steroidal anti-androgens, bicalutamide and flutamide are approved only for use for stage D (metastatic) disease in combination with LHRH agonist therapy whereas the non-steroidal antiandrogen, nilutamide, is approved for use in combination with LHRH agonists or orchidectomy for the treatment of stage C (locally advanced) or D (metastatic prostate cancer). In contrast, the steroidal anti-androgen, cyproterone acetate is approved for the treatment of “advanced” prostate cancer.

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6.1.2 Clinical questions

Androgen deprivation therapy (ADT)

- What should be done for patients with locally advanced disease who are not suitable candidates for surg or radiotherapy – primary androgen deprivation at diagnosis or wait until clinical progression (localized o metastatic) - Timing?
- What should be done for patients with locally advanced disease who are not suitable candidates for surg or radiotherapy – primary androgen deprivation at diagnosis or wait until clinical progression (localized o metastatic)?
- Are there differences between the different hormone therapy methods in the pattern and severity of toxi effects, specifically symptoms such as hot flushes, gynecomastia, liver function and gastrointestinal, effe on sexual function and cognitive function and possible long term side effects such as changes in body composition and metabolic syndrome for non metastatic disease?
- What is the incidence of osteoporosis and reduction in bone mineral density at 2, 5 and 10 years and wh the risk of osteoporotic bone fracture due to bilateral orchidectomy (or orchidectomy), LHRH agonist or l term androgen deficiency?
- What is the effect on Quality of Life as measured by validated questionnaires due to androgen ablation (deprivation or blockade) treatment?

Radiotherapy

- What is the efficacy of external beam radiotherapy techniques for locally advanced disease?

- What is the efficacy of external beam radiotherapy compared with other treatments for local control for locally advanced disease?
- What is the efficacy of radiation for locally advanced disease?

Radiotherapy and androgen deprivation therapy (ADT)

- Is there any survival advantage for androgen blockade (androgen ablation, deprivation) when used as fir line therapy in the adjuvant or neoadjuvant setting with radiotherapy for locally advanced prostate cance
- Are cumulative treatment toxicities different when androgen blockade (androgen ablation, deprivation) is used as first line therapy in the adjuvant or neoadjuvant setting with radiotherapy for locally advanced prostate cancer in locally advanced disease?

Surgery

- What is the evidence that surgery improves the outcomes in men with locally advanced disease?

Surgery plus androgen deprivation therapy

- For men with locally advanced prostate cancer, is there a role for peri-operative hormone therapy in the following situations: neoadjuvant setting, post-radical prostatectomy short duration, post-radical prostatectomy long duration?

Pathologic T3/T4 disease post radical surgery

- What is the efficacy of radiation post radical prostatectomy in patients with extra capsular extension, seminal vesicle involvement or positive surgical margins for locally advanced disease?

Node-positive disease

- Is there any survival advantage for androgen blockade (androgen ablation, deprivation) when used as fir line therapy in the adjuvant or neoadjuvant setting with radiotherapy for locally advanced, node-positive prostate cancer?
- What is the efficacy of radiation for locally advanced node positive disease?

6.1 Introduction

6.1.1 Locally advanced disease

(Locally advanced/high-risk prostate cancer—de novo presentation (clinical stage T3–4, and/or early-stage disease with PSA>20)

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Androgen Deprivation can be achieved in a number of ways. Testicular androgen production can be prevented by surgical castration, by chemical castration through the use of LHRH agonists, or by suppression of androgen production by oestrogens although because of undesirable cardiac side effects oral oestrogens are now rarely used. The other strategy is to use steroidal and non steroidal anti-androgens that compete with both testicular and andrenal androgens for the androgen receptor binding sites. These agents can be used singly and or in combination. It is important to note that there are some restrictions regarding the prescribing of these agents. LHRH agonists are available on the RPBS and anti androgens are only available on the PBS (authority) in combination with ADT. The non steroidal anti-androgens, bicalutamide and flutamide are approved only for use for stage D (metastatic) disease in combination with LHRH agonist therapy whereas the non-steroidal antiandrogen, nilutamide, is approved for use in combination with LHRH agonists or orchidectomy for the treatment of stage C (locally advanced) or D (metastatic prostate cancer). In contrast, the steroidal anti-androgen, cyproterone acetate is approved for the treatment of “advanced” prostate cancer.

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6.1.1.2 Clinical questions

Androgen deprivation therapy (ADT)

- What should be done for patients with locally advanced disease who are not suitable candidates for surg or radiotherapy – primary androgen deprivation at diagnosis or wait until clinical progression (localized o metastatic) - Timing?
- What should be done for patients with locally advanced disease who are not suitable candidates for surg or radiotherapy – primary androgen deprivation at diagnosis or wait until clinical progression (localized o metastatic)?

- Are there differences between the different hormone therapy methods in the pattern and severity of toxi effects, specifically symptoms such as hot flushes, gynecomastia, liver function and gastrointestinal, effe on sexual function and cognitive function and possible long term side effects such as changes in body composition and metabolic syndrome for non metastatic disease?
- What is the incidence of osteoporosis and reduction in bone mineral density at 2, 5 and 10 years and wh the risk of osteoporotic bone fracture due to bilateral orchidectomy (or orchidectomy), LHRH agonist or l term androgen deficiency?
- What is the effect on Quality of Life as measured by validated questionnaires due to androgen ablation (deprivation or blockade) treatment?

Radiotherapy

- What is the efficacy of external beam radiotherapy techniques for locally advanced disease?
- What is the efficacy of external beam radiotherapy compared with other treatments for local control for locally advanced disease?
- What is the efficacy of radiation for locally advanced disease?

Radiotherapy and androgen deprivation therapy (ADT)

- Is there any survival advantage for androgen blockade (androgen ablation, deprivation) when used as fir line therapy in the adjuvant or neoadjuvant setting with radiotherapy for locally advanced prostate cance
- Are cumulative treatment toxicities different when androgen blockade (androgen ablation, deprivation) i used as first line therapy in the adjuvant or neoadjuvant setting with radiotherapy for locally advanced prostate cancer in locally advanced disease?

Surgery

- What is the evidence that surgery improves the outcomes in men with locally advanced disease?

Surgery plus androgen deprivation therapy

- For men with locally advanced prostate cancer, is there a role for peri-operative hormone therapy in the following situations: neoadjuvant setting, post-radical prostatectomy short duration, post-radical prostatectomy long duration?

Pathologic T3/T4 disease post radical surgery

- What is the efficacy of radiation post radical prostatectomy in patients with extra capsular extension, seminal vesicle involvement or positive surgical margins for locally advanced disease?

Node-positive disease

- Is there any survival advantage for androgen blockade (androgen ablation, deprivation) when used as fir line therapy in the adjuvant or neoadjuvant setting with radiotherapy for locally advanced, node-positive prostate cancer?
- What is the efficacy of radiation for locally advanced node positive disease?

6.1.1 Androgen deprivation therapy

Contents

6.1.1.1 What should be done for patients with locally advanced disease who are not suitable candidates for surgery or radiotherapy – primary androgen deprivation at diagnosis or wait until clinical progression (localized or metastatic) - Timing?

Early versus delayed androgen deprivation therapy

Some patients may not be suitable for definitive local therapy because of co-morbidities or advanced age. Data are emerging to provide guidance on the timing of ADT for patients with locally advanced disease and for those with locally advanced disease who decline surgery or radiotherapy. The question for these patients with no evidence of metastases on imaging is whether to start ADT immediately or wait until clinical progression (localised or metastatic).

There is an extensive amount of data addressing this issue, covering the period from the 1970s to 2006. This complicates the analysis because of:

- issues of stage migration and stage detection with pre bone scan and pre PSA era incorporated with studies involving patients who are more accurately staged in modern era
- different treatments from different eras included oestrogens, orchidectomy, anti-androgen monotherapy and luteinising hormone releasing hormone (LHRH) agonist therapy
- heterogeneity of study populations within studies and data findings based on subgroup analyses
- lack of adherence in some studies to study treatment plan (MRC study some controls did not receive treatment on progression)
- the more recent emphasis on the Gleason grade and PSA, doubling time to identify patients with more aggressive disease.

The body of data supporting androgen deprivation appears to be consistent in that immediate treatment shows a disease-specific survival advantage[1], [2] and on occasion an overall survival advantage[2] for men with locally advanced disease. However, the overall impression suggests that if there is a benefit, it is modest. Findings from the two studies cited above were based on subgroup analyses of RCTs that included men with locally advanced disease as well as men with metastatic disease. The VACURG-1[1] study may have included a significant number of men with more advanced disease (asymptomatic metastases) as bone scans were not used for staging. Data would suggest that immediate treatment versus waiting until symptomatic progression is evident does not provide a survival advantage (see chapter 5 Overt metastatic disease and/or loco-regional progressive disease). As a result, any survival benefit for men with truly locally advanced disease only may have been diluted. On the other hand, the overall survival advantage (p=0.02 log rank test) in MRC study of 503 patients with non-metastatic disease was confounded by a significant proportion of the patients not receiving ADT in the deferred arm.[2]

The most informative data in the modern era for the timing of castration therapies comes from two RCTs with similar results. The first study[3] compared immediate versus delayed orchidectomy or LHRH agonists for patients with microscopic (histological or cytological) lymph node (N1–3) positive disease with pathologically confirmed disease who did not undergo a prostatectomy and/or full lymphadenectomy. The study accrued 234 patients who were considered suitable for surgery and prepared for prostatectomy but the prostatectomy was not performed because of lymph node involvement. With a median follow-up of 13 years, there was a hazard ratio of 1.22 (95% CI=0.92 to 1.62) suggesting a possible benefit for immediate therapy.[4] This study was underpowered and did not include men with locally advanced disease considered unsuitable for definitive local therapy.

The second study, a major EORTC study published immediately after 1 April 2006, accrued patients who were not candidates for local definitive treatments due to co-morbid illnesses age and/or advanced local tumour stage, or were refused for local therapy.[5] At a median follow-up of 7.8 years, 541 of 985 patients had died, 193 from prostate cancer and 183 from cardiovascular disease. The overall survival benefit was modest, with a hazard ratio adjusted for a number of factors, including tumour stage, of 1.29 (95% CI=1.09 to 1.53) favouring immediate treatment, seemingly due to fewer deaths from non-prostatic cancer causes. This study was limited for the purpose of this review by the fact that about 50% of the patients did not have locally advanced disease according to the operating definition.

The anti-androgen monotherapy data from a subgroup analysis of a pooled analysis of three RCTs trended towards a survival benefit with anti-androgen therapy when compared with watchful waiting (hazard ratio = 0.81 (0.66 – 1.01) p=0.06) consistent with a treatment effect controlling disease. However this study was potentially confounded by unclear treatment at progression, and use of a class of agent that is less effective as monotherapy in metastatic disease[6] Any benefit (if present) however, has limited clinical applicability to Australia as these drugs are not approved on the PBS as monotherapy.Overall the data suggest there may be a modest benefit for immediate or primary ADT for patients with locally advanced disease deemed not suitable for definitive local therapy. However, decisionshave to be weighed against the impact of ADT on quality of life. This issue is relevant as there is a large number of men with prostate cancer who are not suitable for definitive local therapy and as these studies reflect, this is often a disease found in elderly men.

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6.1.1.2 Evidence summary and recommendations

Evidence summary	Level	References
For locally advanced disease the body of data for androgen suppressive therapy (medical or surgical) appears consistent in that immediate treatment shows a disease-specific survival advantage and on occasion an overall survival advantage. However, the overall impression suggests that if there is a benefit, it is modest.	II	[1], [2], [3], [6], [7]

Evidence-based recommendation	Grade
No strong recommendation can be made for the use of androgen deprivation therapy in locally advanced disease. However, there may be a modest benefit for immediate or primary androgen deprivation therapy for patients with locally advanced disease deemed not suitable for definitive local therapy. However, this has to be weighed against the impact of androgen deprivation therapy on quality of life.	**C**

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6.1.1.4 Appendices

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6.1.2 Early vs delayed androgen deprivation therapy

Contents

6.1.2.1 What should be done for patients with locally advanced disease who are not suitable candidates for surgery or radiotherapy – primary androgen deprivation at diagnosis or wait until clinical progression (localized or metastatic)?

Choice of androgen deprivation therapy

Given the finding that there is possibly a modest benefit for use of primary ADT for locally advanced prostate cancer, it is reasonable to ask whether one therapy is better than another. Again, whilst there is extensive data dating back to the 1970s and the analysis is complicated by the reasons listed in the dot points above. If primary ADT is to be used, data would support castration. There was one RCT and two quasi-randomised trials showing a trend towards higher mortality rates with oestrogens as compared with orchidectomy at four years and longer follow-up[1][2][3][4] and RCTs suggesting a trend towards lower overall survival with anti-androgens alone when compared with medical or surgical castration11 or combined androgen blockade.[5]

This leads to the question as to whether combined androgen blockade (CAB) is better than castration alone for locally advanced disease. There is no definitive comparative trial answering this question in this patient population, with most trials comparing CAB with castration focusing on metastatic disease. Subgroup analyses for patients without evidence of metastatic disease (M0) did not show a survival benefit for combined androgen deprivation for the M0 population[6][5][7]The Prostate Cancer Trialists' Collaborative Group[6] found a small benefit for non-steroidal anti-androgen plus castration in M0 and M1 patients combined (12% M0) but did not analyse separately the effects of adding nonsteroidal anti-androgens for men with non-metastatic disease. Notably, the steroidal anti-androgen, cyproterone plus castration group was slightly worse than castration alone for the combined group of M0 and M1. Therefore, there are no data for or against using CAB for locally advanced disease and the data that do exist suggest no survival benefit. Given the incremental toxicity with CAB, this additional therapy cannot be used without the risk of a detrimental effect on quality of life. Therefore there are no data to mandate CAB if primary ADT therapy is going to be used in patients with locally advanced prostate cancer.

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6.1.2.2 Evidence summary and recommendations

Evidence summary	Level	References
In terms of overall survival there are no data for or against using CAB in preference to medical or surgical castration alone as primary ADT for locally advanced prostate cancer.	I, II	[6], [7], [8]
If primary ADT is to be used, the data would support medical or surgical castration.	II, III-1	[1], [2], [3], [4], [5], [9]

The modest benefit seen with castration alone in the two modern-era studies[10],[11] suggests castration alone can be used as a primary ADT for men with locally advanced prostate cancer. The modest benefit from CAB in the combined M0 and M1 group[6] is at the cost of increased toxicity and may or may not translate to this patient population.

Evidence-based recommendation	Grade
A recommendation cannot be made on the basis of the evidence currently available.	**D**

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6.1.2.4 Appendices

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6.1.3 Complications and cumulative treatment toxicity

Contents

6.1.3.1 Are there differences between the different hormone therapy methods in the pattern and severity of toxicity effects for non metastatic disease?

Complications and cumulative treatment toxicity

For men with non-metastatic prostate cancer, androgen deprivation has been shown to provide a survival benefit as an adjuvant to radiation therapy for high-risk and in many studies for intermediate risk prostate cancer and as an adjuvant to radical prostatectomy but only for lymph node positive fully respected disease.

These treatments may last over two years, with the minimum duration for maximal survival benefit unclear. As a result, adverse events or unwanted effects have the potential to have a significant impact on quality of life. These men have relatively long life expectancies and thus the potential longer-term side effects of these therapies are important. Observational studies have suggested that, with relatively long life expectancies, there may be a higher risk of metabolic syndrome, sudden cardiac death, myocardial infarctions, diabetes mellitus and a higher rate of fractures.[1][2] The longer the duration of ADT with LHRH agonist therapy or orchidectomy, the greater the likelihood of the serious adverse effects of reduced bone mineral density and pathological fracture in particular. (See section 5.1.5 Quality of life for a fuller discussion).

There are a large number of randomised controlled trials reporting ADT adverse events. However, many of these trials are not applicable since medications employed, such as oral oestrogens, finasteride and cyproterone acetate, are not recommended as first-line drugs for prostate cancer, even for short periods to offset the flare effect of LHRH agonists. This review focuses on the adverse events associated with the clinically relevant therapies of castration (medical or surgical) and nonsteroidal anti-androgens for the treatment of non-metastatic prostate cancer.

Five RCTs compared castration (surgical or medical) with no ADT[3][4] [5][6][7][8]; two compared long-term anti-androgen therapy with no ADT[9] [10][11] three compared castration with long-term anti-androgen therapy[12][13] [14] and three compared short-term CAB with no ADT.[15][16][17][18][19]

Limited data from four randomised trials failed to demonstrate an increase in cardiovascular mortality or myocardial infarction with orchidectomy or long-term LHRH agonist treatment.[3][4][5][6] Bicalutamide (anti-androgen) was associated with a significantly increased likelihood of heart failure in one study (risk ratio = 1.96). [20][10]

The effects of castration on sexual function were not reported in these studies, possibly because they are so well accepted. Castration was associated with hot flushes and breast changes[5] and LHRH agonists were associated with cognitive impairment.[7][8]

Increased impotence, hot flushes, gynaecomastia and breast pain, together with tiredness and asthenia were also commonly reported with bicalutamide. [20][10] There was an increased risk of nausea and vomiting with flutamide.[11]

When compared with castration, the non-steroidal anti-androgen, bicalutamide, had similar effects on lipid levels [14], resulted in a smaller increase in body fat mass[13], fewer hot flushes, a lower incidence of decreased libido but an increased incidence of breast changes[12][13][14]. The effects of bicalutamide and LHRH agonist therapy on bone mineral density were highly significantly different at 12 and 96 months; mean bone density decreased with LHRH agonist treatment, but was unchanged with bicalutamide.[13][14]

Short-term CAB was reported not to cause significant increases in cardiovascular mortality[15][16][17][19] [21] severe gynecomastia or liver function abnormalities[19] however in another study 17% of patients who received the anti-androgen flutamide as part of their CAB discontinued flutamide because of liver toxicity.[15][16][17] For a more comprehensive comparison of ADT and castration toxicities see section 5.1.4 Toxity.[15][16][17]

The findings above are consistent with clinical experience for the major toxicities, however, they may understate the problems associated with ADT medications as there are a number of limitations associated with this body of evidence. Firstly, the scope of the problem which is widely known is not addressed; most of the RCTs focused on efficacy outcomes and as a result toxicities and adverse events were rarely evaluated rigorously in terms of scope, and the gamut of well-known adverse effects such as cognitive impairment, liver toxicity and sexual dysfunction were rarely assessed. In addition, using clinical trials to assess adverse events has a number of limitations. As noted by Aronson et al[22], these limitations apply to the ADT trials for prostate cancer and include trials not being large enough to capture rare events, incomplete reporting of adverse events, varying modes of reporting adverse events and differing methods of measuring adverse event. In addition many of these studies were sponsored by the pharmaceutical industry and as such there is the potential for a pervading influence on reporting these 'softer' endpoints of toxicity from a number of studies.

Thus there are limitations in appreciating toxicity in relation to clinical impact of ADT based on this review alone. Evidence of this is provided by the more recent demonstration of the metabolic syndrome as an issue in patients with long-term ADT.[23] There is a need for studies targeting putative side effects as primary end-points and RCTs examining the recently emerging issues of the longerterm problems of cognitive changes, metabolic syndrome and bone loss.

It can be appreciated from the above that there is a significant adverse event profile from ADT, but there are limitations in quantifying exactly the toxicity from ADT and its clinical impact. It is also clear that studies are needed to more accurately define the side effects of ADT as primary end-points and to examine more insidious adverse events, including the longer-term problems of cognitive changes and the metabolic syndrome. New agents such as Receptor Activator of Nuclear Kappa B (RANK) ligand inhibitors, which have recently been shown to prevent bone loss and osteoporotic fractures, have just been evaluated in RCTs in this patient population and are more accurately detailing the impact of ADT on bone health.

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6.1.3.2 Evidence summary and recommendations

Evidence summary	Level	References
For men without clinical evidence of metastatic disease, four trials showed no increase in cardiovascular mortality or myocardial infarction with orchidectomy or long-term LHRH agonist treatment. However, larger population-based studies are required to reveal the small impact. Castration was associated with hot flushes and breast changes (one trial) and cognitive decline (one trial).	II	[3], [4], [5], [6], [7], [8], [10], [11], [20]
Anti-androgens were associated with a significantly increased likelihood of heart failure (bicalutamide), increased impotence, hot flushes, gynaecomastia and breast pain, nausea and vomiting, tiredness and asthenia.	II	[12], [13], [14]
When compared with castration, bicalutamide resulted in smaller increases in body fat mass, fewer hot flushes and a lower incidence of decreased libido, but an	II	

Evidence summary	Level	References
increased incidence of breast changes. Unlike castration, bicalutamide did not decrease bone density at 12 and 96 months.		
Three trials showed no significant increase in cardiovascular mortality with short-term CAB.	II	[15], [16], [17], [19], [24]

It should first be clarified that the recommendations are made with the observation that with the exception of adjuvant therapy with radiation therapy for high-risk and intermediate-risk prostate cancer and lymph node positive fully resected disease, there is no known survival advantage in commencing ADT early (as indicated by increasing serum PSA levels alone after definitive local therapy) rather than later (with radiographically evident metastases). This is particularly important as there is a significant number of unwanted effects (understated in this review) that have a significant impact on quality of life. Therefore, that which is important to the patient should be considered together with his co-morbidities. Specifically, the early commencement of ADT with castration (either as monotherapy or with an anti-androgen) may be more undesirable for individuals for whom sexual activity is very important and for those struggling to cope with declining cognitive abilities or with baseline osteopaenia.

Evidence-based recommendation	Grade
It is recommended that the prescriber take into account the following points when commencing ADT: ■ The use of non-steroidal anti-androgens as monotherapy may have fewer and less severe adverse events than medical or surgical castration but may still have a toxicity profile that impairs quality of life, and there is little to no efficacy data to support their use as monotherapy. ■ Extrapolating from evidence with metastatic disease (see chapter 5 Overt metastatic disease and/or loco-regional progressive disease), Combined androgen blockade (CAB) with an antiandrogen does increase the adverse event profile versus medical or surgical castration monotherapy and this needs to be weighed up against its marginal additional survival benefits seen in patients with metastatic disease. ■ When the unwanted effects of treatment are preferable to the unwanted effects of the tumour (e.g. prevent recurrence with increased overall survival in adjuvant setting), the side-effect profiles of the treatment options should be explained and strategies to minimise these effects should be considered with the patient.	**B**

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6.1.4 Effects on bone health

Contents

6.1.4.1 What is the incidence of osteoporosis and reduction in bone mineral density at 2, 5 and 10 years and what is the risk of osteoporotic bone fracture due to bilateral orchidectomy (or orchidectomy), LHRH agonist or long term androgen deficiency?

Effects on bone health and the risk of fractures

There are numerous studies reporting the effects of medical or surgical castration on bone mineral density (BMD) and fracture rates in men with prostate cancer. Most were observational with results from both prospective and retrospective analyses of hospital and collated organisational data. There were two randomised studies[1][2] comparing changes in BMD in patients randomised to bicalutamide or LHRH agonists. Many studies had industry support, including the two randomised studies that were supported by AstraZeneca.

Measurement methods: Two methods were used to measure BMD changes with Dual Energy X-ray Absorptiometry (DEXA) was the more commonly employed method. However DEXA is not ideal for measuring changes in lumbar spine BMD in older individuals as it does not distinguish aortic calcification and sclerosis of spinal discs and joints known to increase with age.[3] There were fewer manuscripts reporting use of the more sensitive barometer of quantitative computerised tomography (QCT) which, however, exposes patients to more radiation and is subject to quality control issues.

This review focuses on changes in femoral BMD as measured by DEXA and lumbar BMD as measured by QCT. There were a number of other limitations arising out of study designs and the modes of reporting outcomes. The criteria used for reporting changes in BMD varied, reflecting a lack of accepted and standardised or validated yardsticks for men compared with those agreed and accepted for women. Most studies reported the change in mean BMD rather than the incidence of clinically significant decrease in bone mineral density or osteoporosis. Few studies attempted to distinguish osteoporotic fractures from metastatic and traumatic fractures, and the definition of osteoporotic fractures varied. Finally, in comparative studies there were usually baseline differences between the groups that have the potential to confound the results. This was so even when comparing prostate cancer patients with and without ADTs, as ADT may be associated with more aggressive disease or more advanced disease stage. In many studies, disease stage was unclear.

Despite these reservations and the variety of sites at which BMD was measured, the results were consistent in terms of BMD being reduced with LHRH agonists and bilateral orchidectomy, increasingly so over time, but maintained (or slightly increased) with bicalutamide monotherapy. Non-metastatic disease: For men with non-metastatic disease, most studies showed a decline in bone mineral density in the 12 months following initiation of castration therapies. Total hip BMD decreased on average by 3.3 % in a group of 15 men after 12 months of LHRH agonist treatment.[4] This was significantly different from the rise in total hip BMD seen in aged-matched controls (n = 13). In this small study, at least 20% of men were osteopenic at baseline. Declines appeared to continue after 12 months with a 1.95 % decrease in proximal femoral bone mineral density reported for the 12 months after at least 18 months of LHRH agonist treatment.[5] A small case series suggest that combined androgen blockade also results in bone mineral density decreases and that its temporary cessation may induce a temporary stabilisation of bone loss.[6] In contrast oestrogen monotherapy may preserve BMD[7] and there is evidence from two RCTs that the anti-androgen bicalutamide, unlike castration therapies, maintains or increases hip and lumbar spine bone mineral density.[1][2] These data are consistent with the known biology of testosterone depletion and its consequent decrease in oestrogen, and bone mineral depletion.

Metastatic disease: Studies that included men with metastatic disease reported mean decreases in femoral neck bone density of 2.4 – 4.5% in the first 12 months of castration therapies[8][9] and 10% at two years41, with declines continuing to occur after three or more years of treatment.41 In a case series of 50 men, the prevalence of osteoporosis in the lumbar spine rose from 24% at baseline to 48% within six months of starting castration therapies.42 After 12 men with metastatic disease started CAB, femoral neck BMD reportedly decreased on average by 6.5% and lumbar spine BMD by 6.6% at six months.[10]

Osteopaenia, osteoporosis and fractures: The significant clinical impact of BMD changes is based on reports of a considerable background of osteopaenia in patients at baseline, and the reasonable presumption that continuing reductions in BMD predispose patients to clinically meaningful outcomes of osteoporosis and associated pathological fractures. Other risk factors for osteoporotic fractures include decreased muscle strength and frailty, which also may be influenced by androgen deficiency. It is also worth noting that the clinical significance of osteoporotic fracture is greater for hip than for vertebral bodies because of the high mortality rate related to the former. The data showed an increased likelihood of fractures over time with LHRH agonist therapy and bilateral orchidectomy although likelihood estimates varied, reflecting differences in study designs, type of fractures assessed and criteria used. In studies including men with both metastatic and non-metastatic disease, those who underwent orchidectomy had a significantly higher five-year cumulative incidence of osteoporotic fractures (12%) when compared with prostate patients who had not (1%)[11]and a significantly higher risk of an osteoporotic fracture than the age-specific general population, with a standardised incidence ratio of 3.50.[12]

Fractures in non-metastatic disease patients: For men with non-metastatic disease, in a small case series 21% of 81 men receiving castration therapies experienced a non-metastatic fracture over a median follow-up period of 52 months[13]. In two large prospective studies, those who had received LHRH agonists had a significantly higher risk of hip or femur osteoporotic or traumatic fractures (risk ratios reported of 1.76 for a maximum of five years follow-up and 1.36 for a maximum of seven years follow-up)[14][15] and a significantly higher risk (risk ratio = 1.50) of vertebral fractures for seven years maximal follow-up48 when compared with those who had not taken LHRH agonists. These findings are of particular clinical significance as these men without metastatic disease may be destined to live for many years.

The findings are directly applicable to the Australian population to the extent that LHRH agonists and, to a lesser extent, bilateral orchidectomy are the only primary forms of androgen therapy available on the PBS for locally advanced and metastatic disease either as monotherapy or part of CAB. The evidence provided in favour of bicalutamide monotherapy having a BMD-protective property is not relevant as this agent (and class of drug) is not approved for use as monotherapy in Australia.

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6.1.4.2 Evidence summary and recommendations

Evidence summary	Level	References
	III-2, III-3,	[7], [8], [11], [14], [4],

Evidence summary	Level	References
For men with prostate cancer, both LHRH agonists and bilateral orchidectomy significantly reduce bone mineral density, continuing to do so over time, resulting in an increased likelihood of pathological fracture of vertebral bodies and hips from osteoporosis. There is insufficient evidence to make a definite comment on intermittent androgen deprivation.	IV	[5], [9], [10], [12], [6], [13], [16], [17], [18], [19], [20], [21], [22], [23], [24]
There is insufficient evidence to comment on whether there is a worse or diminished effect on BMD with combined androgen blockade (CAB) versus castration monotherapy.	III-2, III-3, IV	
Bicalutamide monotherapy is not associated with reductions in BMD.	II	[1], [2]

Evidence-based recommendation	Grade
Before commencing patients on androgen deprivation therapy, consider the likely duration of that treatment and the risk–benefit analysis for the indication for treatment, and take into account the effects on bone mineral density and risks of pathological fractures from osteoporosis.	**C**

In addition, consider BMD measurements at baseline and subsequently during treatment with the possibility of instituting preventative measures (calcium, vitamin D and exercise) as appropriate for good musculoskeletal health, as well as the use of bisphosphonates as indicated by the Pharmaceutical Benefits Scheme for osteoporosis.

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6.1.5 Androgen ablation treatment and quality of life

Contents

6.1.5.1 What is the effect on Quality of Life as measured by validated questionnaires due to androgen ablation (deprivation or blockade) treatment?

Only three randomised controlled trials comparing different hormone therapies and including men with locally advanced non-metastatic disease examined quality of life outcomes using validated questionnaires.[1][2][3][4][5][6] One trial used the EORTC QLQ C-30 instrument with the prostate cancer supplementary module and the Depression Anxiety Stress Scales, and two trials used the healthrelated QLQ instrument published by Cleary et al.[7] The longest follow-up was only 12 months.[1][2][3][4] 58 None of the instruments used directly assessed the impact of ADT-related symptoms such gynaecomastia and hot flushes on quality of life.

Overall the evidence was limited. There were variations (albeit with a degree of overlapping commonality) in the types of ADTs employed, the instruments used and the numbers of domains assessed and reported. There were also variations in the way in which quality-of-life changes were reported and analysed. Quality of life was not a primary outcome in virtually all of these studies. All were of low quality, with attrition greater than 20% or unclear in two of the three studies.

Different risk and benefit analyses apply to men being treated with long-term adjuvant ADT for locally advanced disease and men being treated with ADT for metastatic disease. One study included patients with metastatic disease as well as locally advanced disease.

For non-metastatic disease there were two studies[1] [3] [4] one (supported by industry) compared bicalutamide with castration, and the other[2] (not supported by industry) compared two LHRH agonists with cyproterone acetate and clinical monitoring. Both studies showed that castration was associated with poorer sexual function than anti-androgen monotherapy. In the bicalutamide study, physical capacity as measured with the Cleary instrument was improved with bicalutamide, however, there were no significant differences in the other eight domains.

Only one study[2] [5] had patients randomised to a non-treatment arm in a clinical environment in which commencement of androgen deprivation was triggered increasingly by a raised PSA for patients not having treatment with curative intent. The numbers in this study are small but they reported a significant increase in emotional distress for the non-treatment arm ($p = 0.002$) with increased sexual dysfunction at one year for all three treatment arms, particularly for goserelin ($p < 0.001$).

In the adjuvant setting, long-term quality-of-life impacts related to therapy, when dealing with the ‘chance of having cancer’, present another paradigm. These studies reported radiotherapy adverse events rather than quality of life outcomes using validated instruments.

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6.1.5.2 Evidence summary and recommendations

Evidence summary	Level	References
Using validated quality of life assessment questionnaires: For non-metastatic prostate cancer there was evidence that medical or surgical castration is associated with poorer sexual function when compared with non-steroidal anti-androgen monotherapy.	II	[1], [3], [4], [5], [2]

Since all quality-of-life studies examined report overall group findings, they should be regarded in a general sense when supporting individual patients in their treatment choices. This relates in particular to timing the commencement of androgen deprivation because of the absence of a clear and significant overall survival benefit with early versus later introduction of ADT.

Evidence-based recommendation	Grade
Toxicities should be considered in the context of what is important to each individual patient, as for some patients impairment of sexual function may have a significant impact on their quality of life and overall adjustment, as well as affecting adversely those close to them.	**C**

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6.1.5.3 References

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6.1.6 Efficacy external beam radiotherapy

Contents

6.1.6.1 What is the efficacy of external beam radiotherapy techniques for locally advanced disease?

Definitive external beam radiotherapy techniques for locally advanced disease

There are nine randomised controlled trials comparing various definitive external beam radiotherapy techniques that include men with locally advanced disease. These studies investigate:

limited versus extended field radiotherapy (three trials)

various dose regimens (four trials), and

conformal versus conventional techniques (two trials).

Limited radiation fields refer to treating the prostate alone with or without the seminal vesicles, whereas extended field radiotherapy includes treating the whole pelvis and in some cases the paraaortic nodes. The dose regimen trials have used various techniques to explore dose-escalated radiotherapy to between 74 and 80Gy compared with the more traditional doses between 64 and 70Gy. 3D conformal radiotherapy refers to the practice of conforming the shape of radiation fields to the prostate (based on CT imaging) in order to reduce dose to critical surrounding tissues.

The studies are variously limited by lack of stratification for types of locally advanced disease, old definitions of locally advanced disease, small numbers, lack of standardisation of endocrine therapy, differences in nodal volumes irradiated, relatively short follow-up, lack of blinding and lack of quality-of-life endpoints. Efficacy outcomes for locally advanced disease are restricted to subgroup analyses and the only toxicity data reported is for entire cohorts of men with T1–4 disease. Overall there are low volumes of good-quality evidence available.

Notwithstanding the above limitations, the two subgroup analyses comparing limited with extended field radiotherapy and examining efficacy outcomes show no differences in efficacy in terms of survival, progression-free survival or metastases.[1][2][3] In the entire cohorts of men with T1–4 disease there are no consistent differences in reported toxicity.[1][2][3][4][5][6] Because of this, it is common practice in Australia to treat limited fields only. However treating the whole pelvis can be justified in selected high-risk patients as at least two of the randomised trials demonstrating the benefit of combining adjuvant ADT with radiotherapy have incorporated whole pelvis radiotherapy.[7][8]

Studies of dose escalation consistently show improved efficacy in terms of freedom from biochemical or clinical failure for high-risk patients[9] [10] including a subgroup of 60 T3 patients.[11] This trend was statistically significant in two of the studies.[10] [11]Late rectal toxicity appears to be worse with higher doses.[10][12][13][14] [15][16][17] For other endpoints there appear to be inconsistent differences.[10] [11]Late rectal toxicity appears to be worse with higher doses.[10][12][13][14][15][16][17][18] There is a potential for dose escalation to have a significant clinical impact by improving efficacy. Further evidence is required in this subgroup of patients.

Studies comparing conformal with conventional radiotherapy are not powered for differences inefficacy. There are inconsistent differences in acute and late toxicities, although the differences that exist all favour conformal radiotherapy.[19][20][21] There is potential to have a significant clinical impact by reducing toxicity. Further evidence is required in this subgroup of patients.

Evolution in technologies has led to refinements in 3D conformal therapies with the introduction of Intensity modulated and image guided radiation treatments (IMRT and IGRT) which allow for better targeting of the prostate and shielding of critical surrounding tissues. These techniques facilitate improved delivery of dose escalated external beam radiation therapy. The results of these newer methods of delivery of treatment will no doubt become available in due course. Furthermore, the role of shortened courses of 3D conformal radiation therapy (hypo-fractionated regimens with biologically equivalent doses) compared with the traditional long courses of conventionally fractionated 3D conformal treatments are also currently being investigated in randomised studies.

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6.1.6.2 Evidence summary and recommendations

Evidence summary	Level	References
There is no evidence to support the routine use of extended field radiotherapy for locally advanced prostate cancer. The role of whole pelvis radiotherapy has yet to be defined. There is some evidence to support the increased efficacy for doseescalated external beam radiotherapy for biochemical and clinical relapse. These data have not yet translated into improved survival or a reduction in distant disease-free survival. There is some evidence that dose-escalation increases toxicity, however, the impact on quality of life is yet to be determined. It is uncertain whether an benefits of dose escalation can be generalised to patients receiving neoadjuvant and/or adjuvant endocrine therapy. There is evidence that conformal radiotherapy decreases toxicity compared with conventional radiotherapy	II	[1], [2], [3], [5], [11], [12], [13], [14], [15], [16], [18], [19], [20], [21], [22]

Evidence-based recommendation	Grade
When radiation therapy alone is used, limited field radiotherapy has similar efficacy and has less toxicity than whole pelvis and therefore is recommended. The role of whole pelvis radiation is yet to be defined. Consideration should be given to dose escalation (74Gy or higher) if it can be delivered safely. Patients with locally advanced prostate cancer should receive 3D conformal radiation to minimise toxicity.	**C**

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6.1.7 External beam radiotherapy vs other treatments

Contents

6.1.7.1 What is the efficacy of external beam radiotherapy compared with other treatments for local control for locally advanced disease?

The management of locally advanced prostate cancer has long been controversial. For patients with a reasonable life expectancy, radiotherapy has traditionally been utilised. More recently, hormonal therapy combined with radiotherapy has been shown to improve outcomes. ADT alone has traditionally been used for locally advanced disease in patients with a poor performance status and/or significant co-morbidities predicting a short life expectancy. Locally uncontrolled disease can be a morbid situation for patients, however, and may cause symptoms related to obstruction, renal impairment, bleeding and pain.

Prior to 2006 (the cut-off date for inclusion of trials for this analysis), there were only three randomised trials comparing radiotherapy with alternative treatment approaches for locally advanced prostate cancer. These all asked different questions, contained small numbers of patients (between 73 and 151 patients), used old techniques, and provided conflicting results.

There was a suggestion of improved survival of radiotherapy over orchidectomy in one study of 151 patients[1][2] but at a cost of increased toxicity. Another study of 73 patients[3] suggested that radiotherapy compared with observation did not delay the first onset of metastases but no long-term follow-up with survival was given. A third study of 95 patients[4] suggested an improvement in progression-free survival with surgery and hormones versus low-dose radiotherapy plus hormones, but at the cost of increased toxicity in the surgery group. Long-term follow-up of the Akakura study published since 2006[5] has demonstrated similar results with a non-significant trend for improved disease-free survival but at increased toxicity.

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6.1.7.2 Evidence summary and recommendations

Evidence summary	Level	References
There are only three randomised trials comparing radiotherapy with alternative treatment approaches for locally advanced prostate cancer. These all asked different questions, contained small numbers of patients, used old techniques, and provided conflicting results. The current body of evidence does not exclude a clinically important benefit with the use of radiotherapy in locally advanced prostate cancer.	II, III-1	[1], [2], [3], [4], [5], [6]

Evidence-based recommendation	Grade
Based on randomised trial evidence, it is not possible to quantify the degree of benefit provided by radiotherapy alone for locally advanced prostate cancer. The role of surgery or hormonal therapy alone in this group of patients remains to be defined.	**D**

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Based on randomised trial evidence, it is not possible to quantify the degree of benefit provided by radiotherapy alone for locally advanced prostate cancer and that the role of surgery or hormonal therapy alone in this group of patients remains to be defined. However, as detailed in the following section on the role of brachytherapy, the totality of data supports the use of androgen deprivation and radiotherapy over radiotherapy alone. The degree of benefit of adding radiotherapy to androgen deprivation was uncertain until a landmark Scandinavian trial was published in The Lancet in January 2009.87 This randomised 875 men with high-risk prostate cancer to hormonal therapy alone (three months of combined androgen blockade followed by indefinite flutamide) or to the same hormonal therapy combined with radiation (3D conformal radiotherapy to prostate and seminal vesicles to dose of 70Gy). Of the cohort 78% had T3 disease and 40% had a PSA>20. With a median follow-up of 7.6 years, there was a 10% improvement in overall survival with the radiotherapy arm (70.4% versus 60.6%). Prostate-specific mortality (for T3 and PSA>20 subgroups as well as the entire cohort) and biochemical control were also improved with the addition of radiotherapy but at the cost of slightly higher rates of urinary, bowel and sexual problems at five years.

Evidence-based recommendation	Grade
Radiation in addition to hormone therapy improves survival and is recommended.	**B**

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6.1.7.3 References

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6.1.8 Brachytherapy

Contents

6.1.8.1 What is the efficacy of brachytherapy for locally advanced disease?

The role of brachytherapy

Brachytherapy involves the implantation or insertion of small ‘sealed sources’ containing a radioactive isotope into the prostate gland either temporarily or permanently. This allows high doses of radiation to be delivered to the prostate gland while minimising doses to adjacent structures such as the rectum and bladder.

There are two main types of brachytherapy commonly used for prostate cancer in Australia:

Permanent implant brachytherapy. This involves the permanent implantation of multiple radioactive seeds (generally Iodine-125 in Australia) directly into the prostate. Seeds are placed through the perineum under ultrasound guidance. In the great majority of cases, low-dose brachytherapy is used as monotherapy for low-to-intermediate risk prostate cancer. There are some institutional series using low-dose brachytherapy as a boost following external beam radiotherapy (EBRT) for locally advanced prostate cancer, but there are no randomised trials evaluating this approach and it is largely viewed as an experimental approach.

Temporary implant brachytherapy. This involves the temporary insertion of a radioactive compound (usually Iridium-192) guided into various positions in the prostate via the placement of multiple catheters that have been placed under ultrasound guidance. It is usually performed in combination with external beam radiotherapy for patients with intermediate- and high-risk cancers. Occasionally lower activity compounds can be used in this way administering radiotherapy over longer time periods (e.g. 24-48 hours)

There is a dearth of good randomised comparative trials to assist in assessing the place of brachytherapy in the treatment of locally advanced disease. There was only one randomised controlled trial that assessed the efficacy of temporary brachytherapy in addition to external beam radiotherapy for locally advanced disease.[1] It was a study of 104 T2-3 patients comparing the use of a temporary brachytherapy 'boost' with an iridium implant (35Gy given in 48 hours) in addition to a course of external beam treatment (40Gy) with external beam treatment alone (66Gy). In the brachytherapy plus EBRT arm, 17 patients (29%) experienced biochemical or clinical failure compared with 33 patients (61%) in the EBRT arm (hazard ratio=0.42; P=0.0024). While this study supported the concept that the addition of HDR like brachytherapy showed 'efficacy', the comparison was not useful to guide contemporary practice as the external beam radiation dose was 66Gy, which has been shown to be inferior to higher doses such as 74Gy.

The results of this and other studies comparing brachytherapy with external radiation are difficult to generalise, since they are essentially comparing the same modality packaged in different ways. There are many other parameters in radiation treatment that affect the disease control probabilities, such as total dose, radiation technique and total treatment time, in addition to the modality of radiation, that is, brachytherapy versus external beam. There are no controls for these in many studies, including the randomised controlled trial, raising the question as to whether one of these other factors might account for any difference seen between the two arms.

In addition, men with locally advanced disease in Australia are generally treated with the combination of androgen deprivation and radiation therapy. There may be interactions with this combination that further confound comparisons.

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6.1.8.2 Evidence summary and recommendations

Evidence summary	Level	References
	II	[1]

Evidence summary	Level	References
There is a paucity of high-quality randomised trial data comparing the use of brachytherapy to surgery for the treatment of locally advanced disease, or indeed comparing the use of brachytherapy radiation to external radiation. There is one medium-quality randomised trial. It provides little evidence to guide contemporary Australian practice, except to the extent it demonstrated evidence of effect of the high dose rate boost. As a result of the study's design it is difficult to draw comparative conclusions from this study.		

Evidence-based recommendation	Grade
3D conformal dose escalated external beam radiotherapy alone, or reduced dose external beam radiation treatment in combination with high dose-rate brachytherapy, are well recognised radical treatments for locally advanced disease. There is no randomised evidence to suggest superiority or to recommend one modality over the other.	**D**

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6.1.8.3 References

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6.1.9 Radiotherapy and androgen deprivation therapy

Contents

6.1.9.1 Is there any survival advantage for androgen blockade (androgen ablation, deprivation) when used as first line therapy in the adjuvant or neoadjuvant setting with radiotherapy for locally advanced prostate cancer?

For the purpose of this chapter we have considered the evidence in terms of short-term (six months or less) and long-term (more than six months) androgen blockade.

Long-term androgen deprivation

Four randomised controlled trials[1] [2][3][4]and two meta-analyses[5][6] fulfilled the eligibility criteria for inclusion in this review. The control arm in these trials was radiotherapy alone. Androgen deprivation consisted of oestrogen[3], LHRH agonist[7][4] and a non-steroidal anti-androgen.[1] Duration of ADT ranged from two years to indefinitely and was commenced with radiotherapy68 or at completion of radiotherapy. The radiotherapy dose to the prostate in three of the trials ranged from 65 to 70 Gy. No data regarding radiotherapy were given in the fourth trial.{{Cite footnote|Citation:McLeod DG, Iversen P, See WA, Morris T, Armstrong J, et al 2006} In two of the trials, pelvic lymph nodes were treated.[7][4][2]/ In all trials the endpoint of overall survival was examined.

These studies showed a statistically significant improvement in overall survival with the exception of the study by Zagars[3], which was a low-quality study using long-term oestrogens. While improved biochemical disease-free survival was also observed, it should be noted that in two of the trials[7][2][3] indefinite ADT was recommended. Biochemical failure in the context of indefinite androgen deprivation most likely represents castrate-resistant disease and these results should therefore be interpreted with caution.

Short-term androgen deprivation

Only one RCT, Trans Tasman Radiation Oncology Group (TROG) 96-01, fulfilled the eligibility criteria for inclusion in this review.[8] This was a three-arm study comparing external beam radiotherapy (EBRT) alone versus three months of hormones plus EBRT (commenced two months prior to radiotherapy) versus six months of hormones plus EBRT (commenced five months prior to radiotherapy). ADT consisted of an LHRH agonist (goserelin) and a

non-steroidal anti-androgen (flutamide). The radiotherapy dose was 66Gy in 33 fractions, which is lower than the current standard dose used in Australia (typically 74Gy). Subgroup analysis of patients with T3–4 disease and patients with PSA>20 was only available for the comparison of EBRT alone versus six months of hormones plus EBRT, with disease-free survival and prostate-cancer-specific survival reported. This demonstrated a statistically significant improvement in disease-free survival with the addition of six months of hormones, but not in prostate-cancer-specific survival.

It should be noted that radiation doses were lower than current standard doses used in Australia and target volumes varied, with several trials treating pelvic lymph nodes. There are no RCTs addressing the use of ADT in conjunction with brachytherapy and it remains unclear as to whether ADT provides a benefit in the era of higher-dose radiotherapy. On a final note, the Radiation Therapy Oncology Group (RTOG) 86–10[9] was not considered in this review as it did not meet inclusion criteria for survival outcomes.

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6.1.9.2 Evidence summary and recommendations

Evidence summary	Level	References
Multiple randomised trials and two meta-analyses show that longterm androgen deprivation in conjunction with radiation improves overall survival. Six months of combined androgen deprivation commencing five months prior to radiotherapy improves disease-free survival. The optimal timing and duration of adjuvant androgen deprivation remains to be defined.	I, II	[5], [7], [8], [1], [4], [2], [3], [6]

Evidence-based recommendation	Grade
It is recommended that patients with locally advanced prostate cancer who are receiving treatment with radical radiotherapy receive long-term androgen deprivation (at least two years).	**B**

Evidence-based recommendation	Grade
Short-term neoadjuvant androgen deprivation therapy can be considered for patients with locally advanced prostate cancer.	**C**

Evidence-based recommendation	Grade
The optimal sequencing and duration of androgen deprivation in relation to radiotherapy is yet to be defined.	**C**

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6.1.9.3 References

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6.1.10 Effect of long-term androgen deprivation on radiotherapy toxicities

Contents

6.1.10.1 Are cumulative treatment toxicities different when androgen blockade (androgen ablation, deprivation) is used as first line therapy in the adjuvant or neoadjuvant setting with radiotherapy for locally advanced prostate cancer in locally advanced disease?

The effect of long-term androgen deprivation on radiotherapy toxicities

Two RCTs assessing long-term androgen deprivation therapy in addition to radiotherapy report radiotherapy toxicity outcomes. The first trial is a comparison of XRT alone versus radiotherapy with three years of LHRH agonist.[1] This trial used whole pelvis radiotherapy. The second trial is a comparison of radiotherapy alone versus radiotherapy with two to five years of a non–steroidal anti– androgen, bicalutamide.[2] No details regarding radiotherapy are available for this trial.

An increase in urinary incontinence (16 versus 29%, p=0.002) with the addition of androgen deprivation therapy was reported in one trial.[1]No increase in acute urinary or bowel toxicity or other late toxicity was reported in this trial. While there was no apparent increase in urinary or bowel toxicity in the second trial[2]they were not assessed for statistical significance.

A recent update of RTOG 85-31 which compared radiotherapy alone with radiotherapy plus indefinite adjuvant androgen blockade also reported no statistically significantly difference in RTOG grade 3–4 genitourinary or gastrointestinal toxicities.[3]

The effect of short-term androgen deprivation on radiotherapy toxicities

Three RCTs assessing short-term ADT in addition to radiotherapy report radiotherapy toxicity outcomes. The first trial, TROG 96-01, is a comparison of radiotherapy alone versus three months and six months of neoadjuvant ADT.[4] [5] The second trial, RTOG 86-01, is a comparison of radiotherapy alone versus radiotherapy with three months of ADT.[6][7] Whole pelvis radiotherapy was used. The third trial is a comparison of radiotherapy alone versus radiotherapy with six months of ADT.[8] In all trials ADT consisted of an LHRH agonist and a non-steroidal anti-androgen, flutamide. All trials were consistent, with no increase in acute or late urinary or bowel toxicity reported with the addition of androgen blockade.

A fourth trial, RTOG 83-07, compared Megestrol versus Diethylstilbestrol.[9] These drugs would not be routinely used as first-line therapy and as such this trial was not considered further.

The effect of short-term versus long-term androgen deprivation on radiotherapy toxicities

One RCT, RTOG 92-02,[10][11] compared short-term with long-term androgen deprivation (four months neoadjuvant plus concurrent LHRH agonist and non-steroidal anti-androgen, flutamide, with or without two years of adjuvant LHRH agonist). This trial used whole pelvis radiotherapy. A statistically significant increase in late RTOG gastrointestinal toxicity grade 3–5 was reported with long-term ADT although absolute rates were low (3 versus 1%, p=0.04) and grade 4 or 5 toxicities were less than 1%.[10] Accounting for differences in reporting of toxicity the evidence suggests that there is no significant increase in radiotherapy toxicity with the addition of ADT. It should be noted that sexual function is inadequately assessed in these studies. Only one trial has reported an increase in late impotence with six months of androgen deprivation.[8]

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6.1.10.2 Evidence summary and recommendations

Evidence summary	Level	References
There does not appear to be any difference in radiotherapy toxicities (urinary and gastrointestinal) with the addition of androgen deprivation therapy to radiotherapy, although it is acknowledged that sexual function has been inadequately assessed in these studies.	II	[4], [5], [6], [8], [7], [1], [2], [10], [11]

Evidence-based recommendation	Grade
Androgen deprivation therapy can be used in combination with radiotherapy without additional radiotherapy toxicities (urinary and gastrointestinal). Effect on sexual functioning	**C**

Evidence-based recommendation	Grade
has not been defined.	

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6.1.10.3 References

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6.1.11 Surgery

Contents

6.1.11.1 What is the evidence that surgery improves the outcomes in men with locally advanced disease?

Surgery for men with locally advanced disease has been rarely reported in the literature. Where it has been performed it has frequently been accompanied by ADT and it has been difficult to separate the effect of the ADT from surgery. It has been possible to identify three randomised studies published prior to 2006 of surgical interventions for the treatment of prostate cancer that included patients with locally advanced disease.

In 1994 Isaka et al[1] reported a randomised trial comparing radical prostatectomy and external beam radiotherapy for men with stage B2 and C disease. Both arms had neoadjuvant and adjuvant endocrine therapy. The follow-up of 100 patients entered was very short, an average of 25 months. There was only one cancer death and no conclusions could be drawn.

Akakura et al 1999[2] published an update of the 1994 study. The follow-up was still relatively short at a median of 58.5 months and given the trial design, it was not possible to isolate the effect of ADT on patient survival. However, the progression-free and cause-specific survival at five years was superiorfor surgery, suggesting that surgery may have provided some benefit over sub-optimal-dose radiotherapy using old techniques. Patients treated with surgery had significantly higher incontinence rates and lower long-term urinary difficulty and gastrointestinal toxicity rates compared to those treated with radiotherapy.

In a more recent update of this trial with a median follow-up of 102 months, surgery was associated with better survival and progression outcomes however none of these benefits were statistically significant.[3]

Biochemical progression-free survival rates for the surgery and radiotherapy groups were 76.2% versus 71.1% respectively. Thus biochemical progression-free rates were better in the surgery group, as were the clinical progression-free rates of 83.5% versus 66.1%, and the cause-specific survival rates of 85.7% versus 77.1%. The overall survival rates were 67.9% versus 60.9%. There was a significantly higher incontinence rate in the surgery group, but no other significant difference in toxicity was reported.

In 2003 Clark et a[4] reported a total of 123 patients who were randomised to an extended node dissection on the right side and a limited dissection on the left. However, only nine patients were T2b or T3 and no long-term survival was reported.

Thomas et al 1992[5] in a small study randomised men with T3 or T4 prostate cancer and urinary retention to transurethral resection of the prostate and orchidectomy, or orchidectomy alone. On the basis of the outcomes of the study, the authors recommended, because of the morbidity associated with the transurethral resection group, that surgery should take place only if the men failed to void after the initial orchidectomy.

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6.1.11.2 Evidence summary and recommendations

Evidence summary	Level	References
For the treatment of locally advanced disease there are no RCTs comparing surgery with modern higher-dose radiotherapy or ADT. For locally advanced disease there are no RCTs examining the efficacy of extended lymph node dissection compared with standard lymph node dissection. In one small RCT for men with urinary retention the addition of TURP to orchidectomy resulted in increased morbidity	II	[5]

Evidence-based recommendation	Grade
There is insufficient evidence to support the use of surgery in the management of advanced prostate cancer, with the possible exception of a transurethral resection of the prostate in men who are unable to void after androgen deprivation therapy.	**C**

6.1.11.3 References

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6.1.12 Surgery plus androgen deprivation therapy

Contents

6.1.12.1 For men with locally advanced prostate cancer, is there a role for peri-operative hormone therapy in the following situations: neoadjuvant setting, post-radical prostatectomy short duration, post-radical prostatectomy long duration?

The management of patients with locally advanced prostate cancer has been influenced by the introduction of androgen deprivation therapy (ADT). This review focuses on patients with locally advanced disease (ie pT3 or higher). Patients with T1 or T2 disease are dealt with in other guidelines.The inclusion of patients with pT3 or higher was due to the older literature studying patients based on volume of disease rather than histological grade. Moreover, patients with bulky (palpable disease) represent a different clinical paradigm. The role of adjuvant ADT with radiation therapy is discussed, refer to clinical question 'Is there any survival advantage for androgen blockage(androgen ablation, deprivation) when used as a first line therapy in the adjuvant or neoadjuvant setting with radiotherapy'.

The use of perioperative ADT in patients with locally advanced disease is discussed in the following clinical contexts:

- neoadjuvant setting
- post-radical prostatectomy short duration (<six months)
- post-radical prostatectomy long duration (>two years)

Fully resected pT3, T4, No/Nx disease

Most of the studies assessing the effects of neoadjuvant ADT focussed on patients with lower-stage disease and thus were excluded from this analysis. Those studies evaluating neoadjuvant ADT for prostatectomy patients with locally advanced disease predominantly reported changes in pathological stage. None was found that assessed survival. As a result, there are no available data on which to base a recommendation on neoadjuvant therapy for locally advanced disease. There is one continuing phase III trial of hormonal therapy plus docetaxel followed by surgery, versus surgery alone, for patients with high-risk disease (including patients with locally advanced disease (CALGB 90203 study).

There were no studies of short duration (six months or less) ADT as an adjuvant to prostatectomy for locally advanced disease. Two low-quality RCTs have examined the effects on survival of prolonged hormonal therapy as an adjuvant to prostatectomy or prostatectomy plus pelvic lymphadenectomy. One was a subgroup analysis and included some patients (4.3%) with radiologically- or biopsy-proven positive nodes.[1] In the other study, patients also underwent a pelvic lymphadenectomy and only those who were pT3–4N0 were included in the study.[2] In both studies the ADT was limited to antiandrogen alone. Neither study showed a survival advantage for anti-androgens alone as post-operative adjuvant therapy for patients with locally advanced disease.[1][2] There were no data for medical or surgical castration as an adjuvant to surgery for fully resected primarily node-negative disease. As a result it is unknown whether the use of castration as adjuvant therapy for patients with marginpositive disease or similar high-risk features will confer a survival advantage. This is the subject of continuing clinical trials.

Microscopic fully resected node positive disease

There was a single RCT examining the effects of long-term adjuvant castration therapy for patients with microscopic fully resected node-positive disease.[3] Unfortunately it was of medium quality as it was not blinded and it was closed early due to poor accrual. It therefore had small numbers and low power. There was a hazard ratio for survival of 3.0 with a median follow-up of 7.1 years18 and 2.14 with longer follow-up (median follow-up of 11.9 years, which was published in June 2006)[4] favouring the long-term ADT arm. The notion of systemic therapy being beneficial is possibly consistent with the benefit seen in patients with high-risk disease treated with ADT and radiotherapy versus radiotherapy alone. The clinical impact of this data set is limited to patients with lymph node positive disease that has been resected. Only patients with pathological node-positive prostate cancer to undergo a lymph node dissection, which further supports performing the procedure in patients with high-risk prostate cancer.

It should be highlighted that the toxicity for patients on androgen deprivation is significant, with unwanted effects in terms of cardiovascular, genitourinary (impotency) systems as well as weight gain and gynaecomastia causing significant problems for a minority of patients (see complications and cumulative treatment toxicity between different hormone therapy methods). The problem of hot flushes was rated as highly significant, affecting 59%.[3] It should be noted that since this publication, a greater awareness of other untoward effects of ADT (such as bone substance loss and its consequences, the metabolic syndrome and cognitive problems) has occurred.

The translation of these data into practice is limited to patients with fully resected lymph node positive disease. It must therefore be emphasised that a lymph node dissection be undertaken. The use of ADT as adjuvant therapy for informed patients with lymph node positive disease in the Australian medical system is applicable, as the PBS requires patients to have ‘locally advanced (equivalent to stage C) disease’ (PBS wording).

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6.1.12.2 Evidence summary and recommendations

Evidence summary	Level	References
Neither of two RCTs for locally advanced disease (pT3–4No/Nx), neither of which showed a survival benefit for post-operative longterm anti-androgen therapy. The effects of castration therapy as an adjuvant to prostatectomy have not been reported in an RCT.	II	[1], [2]
For fully resected node-positive disease there is evidence of overall survival advantage in one study that was closed early.	II	[3]

Evidence-based recommendation	Grade
For locally advanced prostate cancer, anti-androgens as an adjuvant monotherapy to radical prostatectomy are not recommended.	**B**

Evidence-based recommendation	Grade
For node-positive disease androgen deprivation therapy (ADT) should be considered. For patients with fully resected node-positive disease (prostatectomy and lymphadenectomy), it is strongly recommended that patients be counselled on the overall survival benefit of ADT and weighed against the short- and long-term toxicities of androgen deprivation. It is further recommended that patients be counselled on the 'benefit' of improved survival in relation to the 'risk' of therapy – namely the impact of ADT on quality of life.	**C**

The data from this one study for this selected group of patients support use of indefinite ADT. It is not known whether shorter durations (eg three years), such as those found to be beneficial with radiation, carry over to this setting.

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6.1.12.3 References

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3. ↑ [3.0] [3.1] [3.2] Messing EM, Manola J, Sarosdy M, Wilding G, Crawford ED, Trump D. *Immediate hormonal therapy compared with observation after radical prostatectomy and pelvic lymphadenectomy in men with node-positive prostate cancer.* N Engl J Med 1999 Dec 9;341(24):1781-8 Available from: http://www.ncbi.nlm.nih.gov/pubmed/10588962.
4. ↑ Messing EM, Manola J, Yao J, Kiernan M, Crawford D, et al. *Immediate versus deferred androgen deprivation treatment in patients with node-positive prostate cancer after radical prostatectomy and pelvic lymphadenectomy. Cooperative Oncology Group study EST 3886.* Lancet Oncol 2006 Jun;7(6):472-9 Available from: http://www.ncbi.nlm.nih.gov/pubmed/16750497.

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6.1.13 Chemotherapy

See Emerging therapies for ongoing trials in this area.

6.1.14 Bisphosphonates

See Biophosphonate under castration-resistant prostate cancer for a discussion of a single trial of biophosphonates for locally advanced disease.

6.2 Radiation post radical prostatectomy in T3/T4 disease

Contents

6.2.1 What is the efficacy of radiation post radical prostatectomy in patients with extra capsular extension, seminal vesicle involvement or positive surgical margins for locally advanced disease?

The role of post-prostatectomy radiotherapy was not well defined until recently. Historically, post-prostatectomy radiotherapy was not widely adopted primarily due to concerns about toxicity associated with radiotherapy. In addition, there were limited data on the efficacy of radiotherapy post prostatectomy. The recent publication of three randomised controlled trials examining the efficacy of adjuvant radiotherapy post radical prostatectomy in patients with extracapsular extension, seminal vesicle involvement and/or positive surgical resection margins has provided us with a clearer understanding of the benefits of post-prostatectomy radiotherapy.

The European Organisation for Research and Treatment of Cancer (EORTC) 22911 trial randomised 1005 patients and reported their outcomes with a median follow-up of five years.[1] The South Western Oncology Group (SWOG) 8749 trial that randomised 425 men initially presented its results with a median follow-up of 9.7 years[2], but has since updated these results in publications with median follow-up of 10.6 years[3] and 12.7 years[4] respectively. The ARO 96-02 trial randomised 385 men, however only a subgroup of 307 men with an undetectable PSA after surgery was analysed, with a median follow-up of 54 months.[5][6][7]

These trials were similar in respect to entry criteria, radiation dose and techniques. It should be noted that a small percentage of patients in each of the trials received neoadjuvant androgen deprivation therapy (SWOG 8–9%, EORTC 9%, ARO unknown %). The primary endpoint in two of the trials (EORTC and ARO) was biochemical relapse-free survival, however different definitions were used. In the third trial (SWOG) the primary endpoint was metastasis-free survival. Biochemical relapse-free survival was a secondary endpoint. Local control as a secondary endpoint was reported for two of the trials (EORTC and SWOG appendices). These trials were not blinded, however, an intention-to-treat analysis was performed in two of the trials (EORTC and SWOG).

All three trials demonstrated improved biochemical progression-free survival in patients receiving adjuvant radiotherapy (EORTC: hazard ratio=0.48, 98% CI=0.37to0.62, p<0.0001; SWOG: hazard ratio=0.43, 95% CI=0.31to0.58. p<0.001; ARO: hazard ratio=0.49; 95% CI=0.32to0.75, p=0.001). The two trials examining local control also report a statistically significant improvement with adjuvant radiotherapy. While a non-significant trend towards improved metastasis-free survival was initially reported in the SWOG trial, with longer follow-up this has become statistically significant (hazard ratio=0.71, 95% CI=0.54to0.94, p=0.016). In addition, a statistically significant improvement in overall survival has now been demonstrated in those patients receiving adjuvant radiotherapy (hazard ratio=0.72, 95% CI=0.55to0.96, p=0.023).[4]

It is important to note that these trials did not have planned salvage therapy for patients in the observation arm and only 25–50% of patients received salvage radiotherapy. There is some retrospective evidence, such as that by Stephenson et al,[8] that suggests salvage radiotherapy when given early (first sign of PSA failure) may be as effective as adjuvant radiotherapy. This is the subject of continuing randomised controlled trials such as that by the Trans Tasman Radiation Oncology Group (TROG) with the RAVES trial (radiotherapy–adjuvant versus early salvage).

While adjuvant radiotherapy is associated with increased acute radiotherapy toxicity, increased late toxicity,[1][2] rates of serious toxicity are low. In the EORTC trial five-year cumulative incidence rates of grade 3 late toxicities were 4.2% for radiotherapy and 2.6% for the control group (p=0.07); in the SWOG trial[3] 3.3% of radiotherapy patients experienced rectal complications as opposed to none in the control arm (p=0.02), and 18% of radiotherapy patients experienced urethral stricture compared with 10% of control patients (p=0.02). In a small trial (n=107), urinary continence was not significantly affected by post-surgery radiotherapy,[9] however in the larger SWOG trial there was a non-significant increase in urinary incontinence with radiotherapy.[3] While quality of life data from the SWOG study[10] collected up to five years after treatment indicated significantly worse bowel function and urinary frequency post treatment, both appeared to improve with time and global healthrelated quality-of-life, while initially worse, was better at five years in those patients receiving adjuvant radiotherapy.

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6.2.2 Evidence summary and recommendations

Evidence summary	Level	References
There is good evidence to support adjuvant radiotherapy post radical prostatectomy in patients with extra capsular extension, seminal vesicle involvement or positive surgical margins. It is important to note that these trials did not have planned salvage therapy for patients in the observation arm. The role of early salvage radiotherapy is the subject of a recently activated Australian and New Zealand (TROG) randomised controlled trials.	II	[1], [2], [5], [6], [9]

Evidence-based recommendation	Grade
It is recommended that patients with extracapsular extension, seminal vesicle involvement or positive surgical margins receive post-operative EBRT within four months of surgery. The role of active surveillance and early salvage radiotherapy has not been defined.	**B**

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6.2.3 References

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2. ↑ 2.0 2.1 2.2 Swanson GP, Thompson IM, Tangen C, Miller G, Lucia MS, Troyer DA et al. *Phase II randomized study of adjuvant radiation therapy versus observation in pathients with pathologic T3 prostate cancer (SWOG 8794).* International Journal of Radiation Biology 2005.
3. ↑ 3.0 3.1 3.2 Thompson IM Jr, Tangen CM, Paradelo J, Lucia MS, Miller G, Troyer D, et al. *Adjuvant radiotherapy for pathologically advanced prostate cancer: a randomized clinical trial.* JAMA 2006 Nov 15; 296(19):2329-35 Available from: http://www.ncbi.nlm.nih.gov/pubmed/17105795.
4. ↑ 4.0 4.1 Thompson IM, Tangen CM, Paradelo J, Lucia MS, Miller G, Troyer D, et al. *Adjuvant radiotherapy for pathological T3N0M0 prostate cancer significantly reduces risk of metastases and improves survival: long-term followup of a randomized clinical trial.* J Urol 2009 Mar;181(3):956-62 Available from: http://www.ncbi.nlm.nih.gov/pubmed/19167731.
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8. ↑ Stephenson AJ, Scardino PT, Kattan MW, Pisansky TM, Slawin KM, Klein EA, et al. *Predicting the outcome of salvage radiation therapy for recurrent prostate cancer after radical prostatectomy.* J Clin Oncol 2007 May 20;25(15):2035-41 Available from: http://www.ncbi.nlm.nih.gov/pubmed/17513807.
9. ↑ 9.0 9.1 Van Cangh PJ, Richard F, Lorge F, Castille Y, Moxhon A, Opsomer R, et al. *Adjuvant radiation therapy does not cause urinary incontinence after radical prostatectomy: results of a prospective randomized study.* J Urol 1998 Jan;159(1):164-6 Available from: http://www.ncbi.nlm.nih.gov/pubmed/9400462.
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6.2.1 Radiotherapy and adjuvant androgen deprivation therapy

Contents

6.2.1.1 Is there any survival advantage for androgen blockade (androgen ablation, deprivation) when used as first line therapy in the adjuvant or neoadjuvant setting with radiotherapy for locally advanced, node-positive prostate cancer?

The role of radiotherapy for node-positive disease is controversial. There are three RCTs containing subgroups of node-positive (primarily biopsy proven) patients that evaluate any effect of adjuvant androgen deprivation when combined with radiotherapy. Two RCTs examined radiotherapy with adjuvant ADT versus radiotherapy with ADT as a possible treatment on progression. The first, RTOG 85-31, used LHRH agonist until progression[1]. The second used a non-steroidal anti-androgen for a minimum of two years.[2] The third RCT examined radiotherapy with concurrent plus adjuvant ADT (orchidectomy prior to radiotherapy) versus radiotherapy with ADT on progression.[3] The largest RCT, RTOG 85-31, was of medium quality for survival whereas the two smaller RCTs were of low quality. In all three trials the analyses for node-positive disease were unplanned subgroup analyses, increasing the risk that the arms may not be balanced for potential risk factors in this subgroup of patients. The largest subgroup with 173 participants was from RTOG 85-31. The Granfors study contained a subgroup of 39 node-positive patients and the Iversen study contained only 14 patients in their node-positive subgroup.[2] Radiotherapy doses were either not described or varied in all studies.

The RTOG 85-31 and Granfors studies provided data for survival, prostate cancer survival and disease progression. The RTOG 85-31 study showed a trend towards improved survival with 6.5 years median follow-up. A multivariate analysis of patients for whom Gleason scores were available and which took into account Gleason score and whether the men had undergone radical prostatectomy found a statistically significant improvement with adjuvant ADT, with a nine-year survival rate of 62% for adjuvant ADT versus 38% for radiotherapy alone. The smaller Granfors trial with a median follow-up of 9.3 years showed a statistically significant survival benefit for immediate orchidectomy with a nine-year survival rate of 50% for immediate orchidectomy therapy versus 13% for radiotherapy alone.[3] Similar results were found for prostate cancer mortality. With longer follow-up to 19 years, this survival benefit was maintained.[4]The Iversen study had reduced rates of clinical or biochemical progression with anti-androgen therapy in their very small subgroup of men.[2]

Isolated biopsy proven node-positive disease represents a relatively small cohort of prostate cancer patients. In these patients there is potential for a major survival benefit with androgen deprivation in addition to radiotherapy. However it is not known whether adding radiotherapy to androgen deprivation for node-positive patients provides any benefit.

Only one of the three RCTs, RTOG 85-31, examined radiotherapy toxicity outcomes for adjuvant ADT–in this trial LHRH agonist therapy–for the node-positive patient subgroup. The authors reported that the incidence of grade 3 and 4 acute and late toxicities was not statistically significantly different.

As long-term adjuvant androgen deprivation as an adjuvant to radiotherapy appears to improve the survival of men with biopsy node-positive prostate cancer, no evidence of increased radiotherapeutic toxicities would have a substantial clinical impact. However, the hormone-associated toxicities that would have an impact on quality of life were not assessed, reducing the clinical impact.

One trial reports no difference in grade 3 and 4 toxicities with LHRH agonist treatment after radiotherapy. Other known toxicities of hormonal therapy were not reported. [1]

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6.2.1.2 Evidence summary and recommendations

Evidence summary	Level	References
Both of the two larger RCT subgroup analyses for biopsy proven node-positive disease that were examined showed that castration, either LHRH agonist until progression or orchidectomy, resulted in significant overall and cancer-specific survival benefits when combined with radiotherapy	II	[1], [2], [3]

Evidence-based recommendation	Grade
If radical radiotherapy is given to patients with node-positive disease it is reasonable to offer long-term androgen deprivation in addition to radiotherapy..	**D**

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6.2.1.3 References

1. ↑ 1.0 1.1 1.2 Lawton CA, Winter K, Grignon D, Pilepich MV. *Androgen suppression plus radiation versus radiation alone for patients with stage D1/pathologic node-positive adenocarcinoma of the prostate: updated results based on national prospective randomized trial Radiation Therapy Oncology Group 85-31.* J Clin Oncol 2005 Feb 1;23(4):800-7 Available from: http://www.ncbi.nlm.nih.gov/pubmed/15681524.
2. ↑ 2.0 2.1 2.2 2.3 Iversen P, Wirth MP, See WA, McLeod DG, Klimberg I, et al. *Is the efficacy of hormonal therapy affected by lymph node status? data from the bicalutamide (Casodex) Early Prostate Cancer program. Casodex Early Prostate Cancer Trialists' Group.* Urology 2004 May;63(5):928-33 Available from: http://www.ncbi.nlm.nih.gov/pubmed/15134983.

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6.2.2 External beam radiotherapy

Contents

6.2.2.1 What is the efficacy of radiation for locally advanced node positive disease?

There are three randomised control trials examining radiotherapy alone as a treatment option for node-positive disease. Two of the three trials compared prostate and pelvic irradiation to para-aortic and pelvic and prostate irradiation.[1][2][3] The Bagshaw trial included 18 patients and the Pilepich trial, a subgroup analysis, included 134 patients. The third trial was also small, with 77 patients. It compared extended field radiation in pelvic lymphadenectomy patients with observation followed by delayed hormonal therapy.[4]None of the trials was blinded. There were no RCTs comparing conformal modern radiotherapy techniques with immediate hormone therapies.

The trials examining extended field with a more limited pelvic field were consistent, showing no overall survival or disease-free survival benefit when comparing extended para-aortic irradiation to pelvic and prostate irradiation. There was only one trial comparing radiotherapy with no radiotherapy.[4] At five years median disease-free survival was statistically significantly improved in the radiotherapy arm. However, the overall survival benefit with radiotherapy was not statistically significant. The lack of statistical significance may be due to limited follow-up.

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6.2.2.2 Evidence summary and recommendations

Evidence summary	Level	References
The role of external beam radiotherapy in node-positive patients has not yet been defined.	II	[1], [2], [3], [4]

Evidence-based recommendation
There is insufficient evidence to make a recommendation for the use of external beam radiation as alternative or adjuvant to hormone therapies in node-positive patients.

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6.2.2.3 References

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7 Biochemical relapse

Contents

7.1 Biochemical relapse

A significant clinical problem both in terms of frequency and lack of data to provide guidance is the clinical scenario of patients with rising PSA levels and normal testosterone levels following definitive radiotherapy or radical prostatectomy.

- If the PSA rises following definitive local therapy (radical prostatectomy or radiation therapy), this is either due to residual prostatic cancer in the prostatic bed and/or pelvic or distant metastases.
- Very rarely it may be due to residual benign prostatic tissue.
- It also should be realised that after radiation therapy there may be an initial PSA rise ('PSA bounce')[1][2] before PSA declines to a nadir, which can occur as late as two years following treatment. This is commonly seen after seed brachytherapy.

The options for suspected prostate cancer recurrence following localised treatment to the gland with curative intent are further local treatment or systemic therapy in the form of androgen deprivation therapy (ADT). If ADT is going to be given, there is a question as to whether it should be started at the first evidence of PSA rise or when disease is evident with imaging.

However, one must appreciate there are different patient groups in this setting.

- For example, patients with high-risk disease (and most with intermediate-risk disease) that have had definitive radiotherapy with curative intent will have had this in combination with hormonal therapy. In this situation, one needs to distinguish whether their progression is with a normal or castrate testosterone level.
- Another group will be hormone naïve and some of these patients (~20% of men over 60 years) may actually be hypogonadal due to testicular atrophy.[3]
- Some patients after prostatectomy may have received adjuvant radiation therapy and therefore differ to those who have not had prior radiation to the prostatic fossa.

A rising PSA after radiation therapy is also a difficult problem to manage. Local therapy such as resection of the prostate after radiation or other procedures such as cryotherapy can also be considered. However, these are not routine and they have significant risks, such as furthering the chance of incontinence and impotence and, with procedures such as cryotherapy, of fistula (connections) between the bladder and rectum.

It is recognised this a very complicated clinical situation with outcomes predicated by patients' life expectancy, prior therapy and the innate biological characteristics of the cancer (rapid versus indolent). This situation also causes a lot of angst for patients. There are some patients with a very indolent course and the toxicity of early and prolonged ADT may be detrimental.

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7.2 Salvage radiotherapy

Patients who have not had prior radiation therapy are candidates for 'salvage radiation'. These patients are often detected by a PSA rise post-prostatectomy. Salvage radiation is not an option for patients with prior definitive or adjuvant radiation. Unlike adjuvant radiation, there are no randomised phase III trials. The results of 'salvage radiation' are based on retrospective reviews and reported in terms of metastasis-free and overall survival. Patients with a lower PSA level at time of salvage radiation have a better chance of a longer PSA-free survival.[4]There are no randomised controlled data to define the benefits of salvage radiation versus adjuvant therapy or salvage radiation versus systemic therapy (either at time of PSA rise or at time of radiographic progression). The Trans-Tasman Radiation Oncology Group (TROG) is conducting a study of adjuvant radiation versus salvage therapy to help address this unanswered question.

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7.2.1 Clinical questions

- What should be done for patients with rising PSA levels and normal testosterone levels following definitiv radiotherapy or radical prostatectomy?

7.3 References

1. ↑ Horwitz EM, Levy LB, Thames HD, Kupelian PA, Martinez AA, Michalski JM, et al. *Biochemical and clinical significance of the posttreatment prostate-specific antigen bounce for prostate cancer patients treated with external beam radiation therapy alone: a multiinstitutional pooled analysis.* Cancer 2006 Oct 1;107 (7):1496-502 Available from: http://www.ncbi.nlm.nih.gov/pubmed/16944536.
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7.1 Introduction

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7.1.1 Biochemical relapse

A significant clinical problem both in terms of frequency and lack of data to provide guidance is the clinical scenario of patients with rising PSA levels and normal testosterone levels following definitive radiotherapy or radical prostatectomy.

- If the PSA rises following definitive local therapy (radical prostatectomy or radiation therapy), this is either due to residual prostatic cancer in the prostatic bed and/or pelvic or distant metastases.
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The options for suspected prostate cancer recurrence following localised treatment to the gland with curative intent are further local treatment or systemic therapy in the form of androgen deprivation therapy (ADT). If ADT is going to be given, there is a question as to whether it should be started at the first evidence of PSA rise or when disease is evident with imaging.

However, one must appreciate there are different patient groups in this setting.

- For example, patients with high-risk disease (and most with intermediate-risk disease) that have had definitive radiotherapy with curative intent will have had this in combination with hormonal therapy. In this situation, one needs to distinguish whether their progression is with a normal or castrate testosterone level.
- Another group will be hormone naïve and some of these patients (~20% of men over 60 years) may actually be hypogonadal due to testicular atrophy.[3]
- Some patients after prostatectomy may have received adjuvant radiation therapy and therefore differ to those who have not had prior radiation to the prostatic fossa.

A rising PSA after radiation therapy is also a difficult problem to manage. Local therapy such as resection of the prostate after radiation or other procedures such as cryotherapy can also be considered. However, these are not routine and they have significant risks, such as furthering the chance of incontinence and impotence and, with procedures such as cryotherapy, of fistula (connections) between the bladder and rectum.

It is recognised this a very complicated clinical situation with outcomes predicated by patients' life expectancy, prior therapy and the innate biological characteristics of the cancer (rapid versus indolent). This situation also causes a lot of angst for patients. There are some patients with a very indolent course and the toxicity of early and prolonged ADT may be detrimental.

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7.1.2 Salvage radiotherapy

Patients who have not had prior radiation therapy are candidates for 'salvage radiation'. These patients are often detected by a PSA rise post-prostatectomy. Salvage radiation is not an option for patients with prior definitive or adjuvant radiation. Unlike adjuvant radiation, there are no randomised phase III trials. The results of 'salvage radiation' are based on retrospective reviews and reported in terms of metastasis-free and overall survival. Patients with a lower PSA level at time of salvage radiation have a better chance of a longer PSA-free survival.[4]There are no randomised controlled data to define the benefits of salvage radiation versus adjuvant therapy or salvage radiation versus systemic therapy (either at time of PSA rise or at time of radiographic progression). The Trans-Tasman Radiation Oncology Group (TROG) is conducting a study of adjuvant radiation versus salvage therapy to help address this unanswered question.

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7.1.2.1 Clinical questions

- What should be done for patients with rising PSA levels and normal testosterone levels following definitiv radiotherapy or radical prostatectomy?

7.1.3 References

1. ↑ Horwitz EM, Levy LB, Thames HD, Kupelian PA, Martinez AA, Michalski JM, et al. *Biochemical and clinical significance of the posttreatment prostate-specific antigen bounce for prostate cancer patients treated with external beam radiation therapy alone: a multiinstitutional pooled analysis.* Cancer 2006 Oct 1;107 (7):1496-502 Available from: http://www.ncbi.nlm.nih.gov/pubmed/16944536.
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4. ↑ Stephenson AJ, Scardino PT, Kattan MW, Pisansky TM, Slawin KM, Klein EA, et al. *Predicting the outcome of salvage radiation therapy for recurrent prostate cancer after radical prostatectomy.* J Clin Oncol 2007 May 20;25(15):2035-41 Available from: http://www.ncbi.nlm.nih.gov/pubmed/17513807.

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7.2 Rising PSA levels following definitive radiotherapy or radical prostatectomy

Contents

7.2.1 What should be done for patients with rising PSA levels and normal testosterone levels following definitive radiotherapy or radical prostatectomy?

For a more detailed introduction, please read the biochemical relapse section.

If radiation therapy is not undertaken following surgery, the decision would be whether to start hormone treatments due to the rising PSA or wait until metastases become evident through scans. The time to a cancer becoming evident on a scan after a rising PSA is very variable. If the PSA is rising slowly (slow doubling time) and the cancer recurred two years following surgery, only 15% of patients will have cancer seen on a scan at seven years. If however the PSA recurred before two years and the PSA doubled at a rate of less than every 10 months, then 90% of patients have disease on a scan at seven years.[1]

There is only one RCT in this scenario[2] and this involved the use of a 5-alpha reductase inhibitor as a hormonal manipulation with potency sparing properties. The results were presented in terms of change in PSA levels and are of no clinical relevance to routine practice.

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7.2.2 Evidence summary and recommendations

Evidence summary	Level	References
There is no level I or II evidence providing guidance for any intervention.	II	[2]

Evidence-based recommendation
The optimal timing of androgen deprivation therapy in patients with biochemical relapse of disease without evidence of overt metastatic disease is not defined. Eligible patients should be informed about the current TROG Trial comparing early versus delayed hormonal therapy in this group.

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7.2.3 References

1. ↑ Pound CR, Partin AW, Eisenberger MA, Chan DW, Pearson JD, Walsh PC. *Natural history of progression after PSA elevation following radical prostatectomy.* JAMA 1999 May 5;281(17):1591-7 Available from: http://www.ncbi.nlm.nih.gov/pubmed/10235151.
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7.2.1 Optimal Androgen deprivation therapy

Contents

7.2.1.1 Is any one hormone therapy (androgen ablation) superior to another when given in the first line setting in terms of survival in metastatic disease?

When commencing ADT for a patient with locally advanced or metastatic disease, one has to be mindful and counsel the patient on the risks and benefits for the specific clinical situation and the variations of therapy that can be employed. This is especially true when commencing ADT for a man with metastatic hormone-sensitive prostate cancer as the therapy clearly has a side-effect profile that can have an impact not only on quality of life but also the ability to cause disease regression, lessen symptoms from cancer and prolong overall survival.

It is not possible to counsel a patient on how much of an improvement there is on overall survival from ADT versus no ADT because the known efficacy of ADT makes a no-treatment control arm unethical in the metastatic setting. Moreover, as discussed elsewhere, the available data do not demonstrate a clear-cut benefit for starting ADT early or immediately to treat metastatic disease versus waiting until evidence of progression (while under close observation).

The question then arises as to whether one form of hormonal therapy may be better than another in terms of survival outcomes for metastatic disease. This has been addressed in a sensitivity analysis for M1 patients of a single meta-analysis of the numerous trials comparing various hormone therapies with orchidectomy.[1][2] The trials date from the 1970s to the 1990s, a period during which staging with bone scans and PSA levels was evolving, and thus the populations with metastatic disease in these trials may be quite heterogeneous. There has been only one trial published post-2000. Some trials included men with locally advanced disease as well as metastatic cancer and thus subgroup analyses are reported. There are also trials comparing various ADTs with oestrogens. However these were not considered further as oestrogen therapies are associated with increased cardiovascular complications and as a result are not advocated for use as a first-line hormone therapy.

The meta-analysis found that there was no difference in survival between therapies used to induce castrate levels of testosterone (LHRH agonists versus orchidectomy) and that anti-androgens were inferior to orchidectomy with a hazard ratio of 1.13 (95% CI=0.99 to 1.3) for steroidal anti-androgens and 1.25 (95% CI=0.99 to 1.59) for non-steroidal androgens. These data strongly suggest there is a lower overall survival if a patient with metastatic prostate cancer is treated with anti-androgens as monotherapy, be they steroidal or nonsteroidal.

These data therefore inform treating physicians and support current practice that androgen deprivation (medical or surgical castration) can be used interchangeably and that anti-androgens should not be used as monotherapy for patients with metastatic prostate cancer.

In essence, the data indicate that castration-based treatment increases overall survival when compared with less effective therapy and presumably would be better again than no therapy. However, there is at best a minimal survival benefit in commencing ADT early in men with metastatic prostate cancer compared with late commencement of LHRH agonist or bilateral orchidectomy therapy (see early versus delayed androgen deprivation), and these treatments have significant unwanted effects. Therefore judgment should be exercised in relation to the optimal time to introduce these treatments for individual patients with metastatic disease.

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7.2.1.2 Evidence summary and recommendations

Evidence summary	Level	References
For men with metastatic disease: ■ orchidectomy and LHRH agonist have similar effects on overall survival ■ medical or surgical castration appear to provide a survival benefit when compared with anti-androgen (steroidal or non non-steroidal) monotherapy.	I, II	[1], [2], [3], [4], [5]

Evidence-based recommendation	Grade
Patients with metastatic prostate cancer can be treated with either orchidectomy or LHRH agonist based on patient preference. Anti-androgen monotherapy should be avoided as the data indicate this is probably associated with a shorter overall survival.	**C**

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7.2.1.3 References

1. ↑ [1.0] [1.1] Seidenfeld J, Samson DJ, Hasselblad V, Aronson N, Albertsen PC, Bennett CL, et al. *Single-therapy androgen suppression in men with advanced prostate cancer: a systematic review and meta-analysis.* Ann Intern Med 2000 Apr 4;132(7):566-77 Available from: http://www.ncbi.nlm.nih.gov/pubmed/10744594.
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4. ↑ Boccon-Gibod L, Fournier G, Bottet P, Marechal JM, Guiter J, Rischman P, et al. *Flutamide versus orchidectomy in the treatment of metastatic prostate carcinoma.* Eur Urol 1997;32(4):391-5; discussion 395-6 Available from: http://www.ncbi.nlm.nih.gov/pubmed/9412794.
5. ↑ Schröder FH, Kurth KH, Fosså SD, Hoekstra W, Karthaus PP, et al. *Early versus delayed endocrine treatment of pN1-3 M0 prostate cancer without local treatment of the primary tumor: results of European Organisation for the Research and Treatment of Cancer 30846--a phase III study.* J Urol 2004 Sep;172(3): 923-7 Available from: http://www.ncbi.nlm.nih.gov/pubmed/15310999.

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7.2.2 Single agent versus total androgen blockade

Contents

7.2.2.1 Is there any survival advantage for maximum androgen blockade (or combined hormone therapy) compared with single agent androgen blockade when used as first line therapy in metastatic disease?

Castration therapies are effective but temporary therapies for metastatic disease, but are justifiable in context of preventing potential androgen “flare” to avoid further impingement if there were other areas of metastatic disease that may already be causing significant but not clinical evidence of cord compression. Numerous RCTs have examined whether combined androgen blockade (CAB) might provide a survival benefit when compared with castration monotherapies in the treatment of metastatic (M1) prostate cancer. Most of these trials have been the subject of three meta-analyses[1][2][3], with the largest of these[3] following up all 8275 participants in 27 RCTs.

There is some heterogeneity in study design in this extensive body of literature, It includes some trials using steroidal anti-androgens and others using non-steroidal anti-androgens in combination with orchidectomy or LHRH agonist. Another source of heterogeneity was the inclusion in some studies of patients with locally advanced disease (M0) along with patients with radiographic evidence of disease (M1). However, over 80% of men included in the largest meta-analyses had metastatic disease.

The overall results of the meta-analyses demonstrate either no significant benefit[3] or only a small benefit {{Cite footnote|Citation:Samson DJ, Seidenfeld J, Schmitt B, Hasselblad V, Albertsen PC, Bennett CL, et al 2002} when results for both steroidal and non-steroidal anti-androgens were combined. The inconsistencies could be explained by the heterogeneous nature of the studies. More specifically, however, the use of cyproterone acetate appears to be detrimental (the difference in mortality rates was 2.8%) in the largest meta-analyses[3] whereas non-steroidal anti-androgens were associated with a modest but significant improvement, with a difference in mortality rates of 2.9%[3] and an odds ratio for overall survival of 1.29 at five years[1]

The number of patients who die of metastatic prostate cancer each year (second leading cause of male cancer deaths) and the overall survival benefit indicates that these data are of significant clinical relevance. The modest increase in overall survival, however, is balanced against the increased side effects of adding a non-steroidal anti-androgen to androgen deprivation (castration) therapy and this limits the clinical impact or usability of combined androgen blockade for all patients.

The data can be directly generalised to patients with metastatic prostate cancer as both LHRH agonists and anti-androgens are on the PBS for this indication and orchidectomy is an easily accessible procedure.

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7.2.2.2 Evidence summary and recommendations

Evidence summary	Level	References
There appears to be a small but significant benefit from adding a non-steroidal anti-androgen to androgen deprivation therapy. This is a class effect in favour of non-steroidal anti-androgens. In contrast, there appears to be a detrimental effect with the use of the steroidal anti-androgens. However, the benefit is modest and it required a large number of clinical trials to come to this finding.	I, II	[1], [2], [3], [4], [5], [6], [7], [8], [9]

Evidence-based recommendation	Grade
Patients with metastatic prostate cancer may be treated with a non-steroidal anti-androgen combined with androgen deprivation therapy as a continuing strategy (beyond the period of LHRH-induced surge [flare] of testosterone) if they are prepared to accept the greater likelihood of unwanted effects from combination therapy.	**B**

Evidence-based recommendation	Grade
It is recommended that patients with high–volume disease or disease where urgent tumour debulking is required (eg impending spinal canal compression or urinary outflow obstruction) be commenced on combined androgen blockade to prevent flare reactions. This required period is approximately one month for an LHRH agonist and covers the time it takes for testosterone levels to reach a castrate state. Continuation of combined therapy beyond that period may be considered if the patient is prepared to accept the greater likelihood of unwanted side effects from combination therapy.	

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7.2.2.3 References

1. ↑ 1.0 1.1 1.2 Schmitt B, Bennett C, Seidenfeld J, Samson D, Wilt T. *Maximal androgen blockade for advanced prostate cancer.* Cochrane Database Syst Rev 2000;(2):CD001526 Available from: http://www.ncbi.nlm.nih.gov/pubmed/10796804.
2. ↑ 2.0 2.1 Samson DJ, Seidenfeld J, Schmitt B, Hasselblad V, Albertsen PC, Bennett CL, et al. *Systematic review and meta-analysis of monotherapy compared with combined androgen blockade for patients with advanced prostate carcinoma.* Cancer 2002 Jul 15;95(2):361-76 Available from: http://www.ncbi.nlm.nih.gov/pubmed/12124837.
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6. ↑ Tyrrell CJ, Altwein JE, Klippel F, Varenhorst E, Lunglmayr G, Boccardo F, et al. *Multicenter randomized trial comparing Zoladex with Zoladex plus flutamide in the treatment of advanced prostate cancer. Survival update. International Prostate Cancer Study Group.* Cancer 1993 Dec 15;72(12 Suppl):3878-9 Available from: http://www.ncbi.nlm.nih.gov/pubmed/8252508.
7. ↑ Tyrrell CJ, Altwein JE, Klippel F, Jurincic-Winkler C, Varenhorst E, Lunglmayr G, et al. *Comparison of an LH-RH analogue (Goeserelin acetate, 'Zoladex') with combined androgen blockade in advanced prostate cancer: final survival results of an international multicentre randomized-trial. International Prostate Cancer Study Group.* Eur Urol 2000 Feb;37(2):205-11 Available from: http://www.ncbi.nlm.nih.gov/pubmed/10705200.

8. ↑ Ansari MS, Gupta NP, Hemal AK, Dogra PN, Seth A. *Combined androgen blockade in the management of advanced prostate cancer: a sensible or ostensible approach.* Int J Urol 2004 Dec;11(12):1092-6 Available from: http://www.ncbi.nlm.nih.gov/pubmed/15663681.
9. ↑ Kotake T, Usami M, Akaza H, Koiso K, Homma Y, Kawabe K, et al. *Goserelin acetate with or without antiandrogen or estrogen in the treatment of patients with advanced prostate cancer: a multicenter, randomized, controlled trial in Japan. Zoladex Study Group.* Jpn J Clin Oncol 1999 Nov;29(11):562-70 Available from: http://www.ncbi.nlm.nih.gov/pubmed/10678560.

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7.2.3 Early versus delayed androgen deprivation

Contents

7.2.3.1 For patients with radiologically detectable but asymptomatic disease should hormone therapy be started immediately or should it be started at the onset of symptoms?

One clinical scenario is the management of patients with radiographic evidence of disease without symptoms. The question arises as to whether ADTs should be started immediately or delayed until the onset of symptoms. Two RCTs have addressed this question. These trials took place in different eras. One trial, VACURG-1, was performed in the 1960s and 1970s[1], while the MRC Prostate Cancer Working Group study was undertaken in the 1980s and 1990s.[2] This complicates the analysis because of:

- issues of stage migration and stage detection with pre bone scan and pre PSA era incorporated with studies of patients who are more accurately staged in the modern era
- different treatments from different eras included oral oestrogens, orchidectomy and LHRH agonist therapy.

In addition, both studies included men with non-metastatic as well as metastatic disease. As a result data findings were based on sub-group analyses, and in the MRC trial the study plan was not always adhered to, with some controls not receiving treatment on progression.

In both RCTs, no clear survival benefit was shown for patients who started castration therapy with symptoms versus those who started therapy when no symptoms were present. This data set is limited as the VACURG study may have included a proportion of patients with symptoms and the MRC study was confounded by some patients in the delayed therapy arm not receiving therapy.

This would suggest there is not a mandate to commence ADT in patients with asymptomatic metastases. It should be noted that the MRC and VACURG-1 studies are not therapy versus no therapy since such studies would be unethical. ADT is an effective therapy for metastatic disease (albeit temporarily) and patients can be salvaged at the time of symptomatic progression.

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7.2.3.2 Evidence summary and recommendations

Evidence summary	Level	References
The limited data suggest patients with asymptomatic metastatic prostate cancer are not advantaged by early androgen deprivation therapy until symptomatic progression.	II	[1], [2]

Evidence-based recommendation	Grade
Androgen deprivation therapy is indicated for metastatic prostate cancer. Immediate therapy is warranted for symptomatic metastases. The evidence for immediate therapy for asymptomatic metastases is unclear, but it is definitely warranted if delay may result in complications (eg spinal cord compression from vertebral metastases).	**C**

A decision about whether to defer therapy for patients with asymptomatic metastases will be a discussion between patient and physician. Patients will require close follow-up if therapy is deferred. Close evaluation would include an MRI of the spine for patients with documented but asymptomatic vertebral metastases to ensure there is no pending spinal canal encroachment which would necessitate more urgent treatment.[3]

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7.2.3.3 References

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3. ↑ Venkitaraman R, Sohaib SA, Barbachano Y, Parker CC, Huddart RA, Horwich A, et al. *Frequency of screening magnetic resonance imaging to detect occult spinal cord compromise and to prevent neurological deficit in metastatic castration-resistant prostate cancer.* Clin Oncol (R Coll Radiol) 2010 Mar; 22(2):147-52 Available from: http://www.ncbi.nlm.nih.gov/pubmed/20034772.

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7.2.4 Toxicity

Contents

7.2.4.1 Are there differences between the different hormone therapy methods in the pattern and severity of toxicity effects in metastatic disease?

Numerous trials examining hormone therapy as a treatment for metastatic disease reported adverse events and toxicities. Many included patients without clinical metastatic disease and as a result patient populations were often markedly heterogeneous. Furthermore, the duration of follow-up ranged from less than six months to many years and, in a number of studies, this was unclear. Finally, as with the trials of ADT for non-metastatic disease, most of these RCTs had the limitations of focusing on efficacy outcomes rather than toxicities with adverse events. The latter were rarely comprehensively recorded and evaluated rigorously and so are potentially understated. A final concern is that many studies were sponsored by the pharmaceutical industry and this may have introduced a bias.

Early versus delayed androgen deprivation

There were three RCTs comparing immediate castration with delayed treatment that included patients with metastatic disease. Two of these studies included patients with M0 disease and the third was a M1 subgroup analysis. Two examined cardiovascular mortality and one examined haemoglobin levels. Castration did not significantly increase cardiovascular mortality[1][2] [3], however it did cause a significant decrease in haemoglobin levels.[4]

CAB versus monotherapy

As cyproterone accetate is not recommended for first-line ADT by the UK Committee on the Safety of Medicines and in the ASCO Guidelines, this medication was not considered. Despite this exclusion, the overall body of evidence comparing CAB with castration is considerable. Five RCTs examined the addition of nilutamide to castration; 11 RCTs examined the addition of flutamide to castration; one RCT examined the addition of bicalutamide to castration. Only patients with metastatic disease were included in the nilutamide trials. The addition of anti-androgens did not significantly increase the risk of cardiovascular adverse events (nilutamide, three trials; flutamide, three trials). The addition of flutamide significantly increased the incidence of liver abnormalities in three of six trials and significantly increased hot flushes in one[5] of nine trials. Nilutamide did not significantly affect the incidence of hot flushes (three trials) while bicalutamide appeared to decrease the incidence of hot flushes.[6] In a single trial, nilutamide had no effect on gynecomastia. However, flutamide appeared to increase the incidence of breast changes, with one of the seven trials of flutamide showing a significant increase in gynecomastia.[7] Nilutamide did not appear to affect gastrointestinal symptoms (four trials) whereas four of eight trials showed a significant increase in gastrointestinal side effects with the addition of flutamide. There was a trend towards decreased flare with anti-androgens and this was almost significant in the only nilutamide trial examining flare and in one of the four flutamide trials examining flare. Anaemia was significantly increased with flutamide[8], whereas anaemia and asthenia decreased with nilutamide.[9] Nilutamide is also reported to be associated with alcohol intolerance and night blindness. In terms of clinically relevant studies, there are many trials with a CAB arm, particularly with flutamide and more recently, bicalutamide, as these two drugs had the benefit of patent protection and hence the motivation of industry to support studies looking to define a clinical advantage for these agents.

Different therapies

There were a large number of RCTs comparing different hormone therapies for metastatic disease. Many of the treatments, such as oestrogens, LHRH agonists triptorelin and buserelin nasal spray, the LHRH antagonist abarelix and the steroidal anti-androgen chlormadinone acetate are not approved or listed by the Pharmaceutical Benefits Scheme (PBS) for use in Australia. When studies involving these drugs are removed, the volume of evidence is good rather than excellent. This review focuses on castration (surgical or medical) and peripheral blockade (anti-androgen or cyproterone) in order to provide a discussion that is relevant to current practice.

There were five RCTs comparing non-steroidal anti-androgens with castration[10][11][12][13][14] one RCT comparing cyproterone acetate with castration[15], one RCT comparing the non-steroidal anti-androgen, flutamide with cyproterone acetate[16] and one RCT comparing flutamide with bicalutamide as part of CAB therapy.[17][18][19]

There is a general consistency in findings in a majority of studies, although this is not universal.

Sexual activity

Three of the four trials comparing bicalutamide with castration used the lower 50mg dose.[11][12][20] In these studies sexual dysfunction was reported as part of a quality of life assessment. Cyproterone acetate and flutamide did not differ significantly in their effects on sexual activity, with over 70% of patients experiencing a loss of sexual activity.[16][21]

Liver abnormalities

Only one study comparing non-steroidal anti-androgens with castration reported results for liver dysfunction. In that trial there was no significant difference in liver toxicities.[10] The trial was small and would not have been sufficiently powered to detect significant differences in the incidence of rare events, such as liver dysfunction. Its findings contrast with warnings of an increased risk of liver toxicities with anti-androgens, which are acknowledged in product information documents and apparent in trials comparing CAB with castration. This apparent anomaly highlights the paucity and possible limitations of the randomised evidence for this adverse event and more broadly, the importance of reporting adverse events to agencies such as the Adverse Drug Reactions Advisory Committee (ADRAC) and post-marketing surveillance. Liver toxicity was significantly higher with flutamide compared with cyproterone acetate.[16][21]The incidence of abnormal liver function tests did differ significantly when flutamide was compared with bicalutamide.

Hot flushes

In all five RCTs there was a significantly lower risk of hot flushes with non-steroidal anti-androgens compared with castration. The incidence of hot flushes did not differ significantly between cyproterone acetate and flutamide or bicalutamide and flutamide.

Gynaecomastia and breast tenderness

In all five RCTs there was a significantly higher risk of gynaecomastia and/or breast tenderness with non-steroidal anti-androgens compared with castration. The incidence of gynaecomastia was also significantly higher with flutamide compared with cyproterone acetate.

Gastrointestinal disturbances

Three of the five studies showed a significant increase in gastrointestinal adverse events with bicalutamide compared with castration. Flutamide was associated with a higher risk of diarrhoea when compared with bicalutamide.

Asthenia/fatigue

One of two trials found increased asthenia with bicalutamide compared with castration and, for patients also receiving leuprolide, flutamide carried a significantly higher risk of anaemia than bicalutamide

Cardiovascular morbidity

No increase in cardiovascular mortality was reported in non-oestrogen trials. This concern is more relevant for patients treated for risk relevant disease with rising PSA, no metastases and expected indolent course, rather than patients with metastatic disease needing anti-cancer therapy to prolong overall survival and prevent cancer complications.

Cognitive function

Although there are no randomised cognition studies of patients with metastatic prostate cancer, those few undertaken with patients with non-metastatic disease are applicable. Thus a significant proportion of patients receiving ADT can be expected to have adverse cognitive changes such as impaired memory, attention and executive functions.

The fact that toxicities are only secondary end-points in most studies and the uncertain influence of industry (e. g. to possibly downplay the significance in data analysis and reporting) in many of the trials raise the possibility that toxicities are understated, as substantiated by the relative recent awareness of some of these problems (as mentioned above).

As stated above, many of the trials published do not relate to the Australian health care environment. Bilateral orchidectomy and LHRH analogue therapy are recognised and approved by the PBS for ADT monotherapy, as is the steroidal anti-androgen cyproterone acetate and non-steroidal agents bicalutamide, flutamide and nilutamide. However, because of its toxicity profile, cyproterone is not recommended by several bodies to be suitable as first-line ADT therapy (either alone or in combination with castration). The anti-androgens bicalutamide and flutamide are approved for use in combination with LHRH agonists (to offset flare effect and as part of CAB as a longer-term strategy), with nilutamide also approved for use with bilateral orchidectomy to achieve CAB.

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7.2.4.2 Evidence summary and recommendations

Evidence summary	Level	References
Castration did not significantly increase cardiovascular mortality (two trials). However, it did cause a significant decrease in haemoglobin levels (one trial).	II	[1], [2], [3], [6]
The addition of non-steroidal anti-androgens to castration can result in an additive increase in toxicities that impair quality of life, such as hot flushes and gynaecomastia, as well as liver function	II	[10], [16], [5], [7], [8], [9], [11], [12], [13], [22], [20], [15], [21], [17], [18], [19], [23], [24], [25], [26], [27], [28], [29], [30]

Evidence summary	Level	References
abnormalities. With respect to the most common unwanted effects of androgen deprivation therapy: ■ **hot flushes** are common following all androgen deprivation therapies, though less so with anti-androgens as monotherapy, ■ **gynaecomastia** and nipple tenderness are a feature of all ADTs but more so with anti-androgens ■ **liver function and gastrointestinal side-effects**: abnormal liver function tests (LFTs) are a class-effect problem with antiandrogens; diarrhoea is stated to be a troublesome sideeffect from flutamide ■ **Cardiovascular morbidity**: no increase cardiovascular mortality was reported in non-oestrogen trials. ■ **other side effects**: tiredness and anaemia are commonly reported.		

Evidence-based recommendation	Grade
The benefits of androgen deprivation therapy in controlling a patient's cancer outweigh the ADT adverse-event profile. However, given the clinically relevant and quality-of-life impairing litany of unwanted effects of ADT, the timing of commencement of ADT as a palliative treatment needs to be considered carefully. Assessment of liver function tests, risk of osteoporosis and bone density measurements as required is recommended. Baseline information on what is important to each individual patient should be ascertained (refer chapter 3, p20). This will permit the commencement and nature of treatment to be tailored and allow an assessment of the cause of adverse effects if they emerge. The common side effects need to be discussed with the patient before commencing any ADT. All patients taking anti-androgens should have their liver function tests monitored.	**C**

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7.2.5 Quality of Life

Contents

7.2.5.1 What is the effect on Quality of Life as measured by validated questionnaires due to androgen ablation (deprivation or blockade) treatment in metastatic disease?

Seven randomised controlled trials comparing different hormone therapies and including patients with metastatic disease examined quality of life outcomes using validated questionnaires. The questionnaires used were the SWOG QLQ and SF-36 instruments (one trial) and the health-related QLQ instrument published by Cleary et al[1](six trials). None of these directly assessed the impact of hormone symptoms such as gynaecomastia and hot flushes on quality of life.

Overall the evidence was limited, with variations in the types of ADTs employed (albeit often featuring bicalutamide as the anti-androgen), numbers of domains assessed and reported, albeit with a degree of overlapping commonality, and the way in which quality-of-life changes were reported and analysed. Quality of life was not a primary outcome in virtually all of these studies. The majority of studies have an association with industry, particularly Zeneca/AstraZeneca. Their influence is impossible to ascertain. All were of low quality, with only two studies blinded and over 20% attrition in most studies.

Quality of life studies in the metastatic setting, given the presence of active cancer and managing cancer complications, have a different risk–benefit ratio versus quality of life studies in an adjuvant context. In these studies, few quality of life domains differed significantly with different hormone therapies. Studies comparing anti-androgen versus castration give an overall impression that sexual function was less affected than by castration, which makes biological sense but must be balanced by improvements in cancer control.

Combined androgen blockade with flutamide, when compared with orchidectomy alone, was associated with significantly more diarrhoea but better mental health scores in the first six months.[2] As part of maximal androgen blockade treatments, flutamide when compared with bicalutamide had better physical capacity outcomes.[3]

As cyproterone acetate is not recommended as first-line ADT either as monotherapy or in combination, and non-steroidal anti-androgens such as bicalutamide are not recommended or approved by the PBS as monotherapy, only the results dealing with combined androgen blockade for metastatic disease are applicable.

As stated above, the unknown extent and influence of industry in so many studies increases the difficulty in making objective evaluations.

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7.2.5.2 Evidence summary and recommendations

Evidence summary	Level	References
Using validated quality of life assessment questionnaires: ■ for metastatic disease there was evidence that castration is associated with poorer sexual function when compared with non-steroidal anti-androgen monotherapy ■ combined androgen blockade with flutamide when compared with orchidectomy alone was associated with more diarrhoea but better mental health scores ■ as part of maximal androgen blockade treatments flutamide had better physical capacity outcomes than bicalutamide.	II	[3], [4], [5], [6], [7], [8]

Since all the quality of life studies examined report overall group findings, they should be regarded in a general sense when supporting individual patients in their treatment choices. This relates in particular to the timing of the commencement of androgen deprivation because of an absence of a clear and significant overall survival benefit with early versus later introduction of ADT.

Evidence-based recommendation	Grade
Toxicities in the context of what is important to each individual patient should be considered, as decrements in highly valued faculties for some patients may have a significant impact on the quality of life and overall adjustment of those individuals and those close to them.	**C**

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7.2.5.3 References

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7.2.6 Intermittent or continuous androgen deprivation therapy

Contents

7.2.6.1 Is there a difference in survival for intermittent androgen deprivation compared to continuous androgen deprivation?

As stated previously, ADT is associated with a number of toxicities that are quality-of-life impairing and/or clinically significant and are related to prolonged exposure to castrate level of testosterone. This is particularly relevant for patients who have a good initial response to therapy that portends the potential for long-term benefit from ADT. A strategy to potentially ameliorate the toxicity is to use ADT intermittently (ie withhold when in remission and restart when regrowth occurs). It is also contended, based on preclinical models, that the cyclical exposure to ADT and testosterone will prolong the sensitivity to ADT and hence increase the efficacy of ADT. At the time of writing, the volume of evidence was limited by:

- lack of data from reported large well-powered randomised studies, that is, the definitive studies are yet to be reported and only smaller studies have been reported
- inclusion of locally advanced (M0) patients along with patients with evidence of metastatic disease (M1) and thus poorer prognoses
- findings based on subgroup analyses of the use of differing hormonal therapies such as cyproterone and non-steroidal antiandrogens with LHRH agonists the use of differing hormonal therapies such as cyproterone and non-steroidal antiandrogens with LHRH agonists
- reporting on progression-free survival whereas overall survival is the more meaningful and reliable endpoint, especially when balanced by quality-of-life data. Specifically, time to PSA (biochemical) progression as an endpoint is not clinically relevant.

The current data with all the caveats listed above have some degree of consistency as they suggest there is no detriment to intermittent versus continuous androgen deprivation. However, the data from well-powered studies are yet not mature enough to comment on improvement in overall survival and time to symptomatic progression. At best, the current data suggest there is no decrease in long-term disease control or overall survival for men with non-metastatic or metastatic disease[1][2][3][4] and that there may be an improvement in quality of life (potency, hot flushes).[2][5][6][7]

Once the final data are available they will be of major importance as a substantial number of patients with metastatic prostate cancer commencing ADT are treated with LHRH agonists (as opposed to orchidectomy) and do achieve a good initial remission with ADT. As such, the more commonly employed mode of androgen deprivation and the number of patients who would be candidates for an intermittent approach makes this an approach possibly relevant in clinical practice. Therefore the data can be directly generalised to the target population with the caveat that larger and better-powered definitive studies to quantify the benefit still await analysis. The mode of therapy required to implement intermittent ADT is readily accessible through the PBS (ie LHRH agonists), so if the definitive datasets confirm its benefit, the data will be directly applicable in the Australian health care context.

Note: Larger well-powered studies have been completed and will clarify the benefit of this approach. Thus the current statements regarding the current data are laced with caveats pending the definitive datasets.

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7.2.6.2 Evidence summary and recommendations

Evidence summary	Level	References
The data as of the time of the cut-off are limited but appear to suggest a benefit with lessening of some of the side effects of the androgen deprivation therapy without compromising long-term disease control. However, the quality of life data are limited by the lack of a placebo comparator.	II	[1], [3], [5], [5], [7]

Evidence-based recommendation	Grade
No formal recommendation on intermittent or continuous androgen deprivation therapy can be made based on the lack of definitive data. However, it would appear that there may be a quality of life benefit. Intermittent androgen deprivation therapy can be considered for men who (i) achieve a good remission, (ii) are destined to be on ADT for a prolonged period, and (iii) are having intolerable side effects from long-term androgen deprivation.	**C**

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7.2.6.3 References

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7.2.7 Radiotherapy treatment of bone pain

Contents

7.2.7.1 What is the effectiveness of local external beam radiotherapy (EBRT) in the palliation of uncomplicated bone pain?

Treatment of bone pain

No trials specific to prostate cancer were identified. Most trials have accrued patients with any commonly seen malignant diseases associated with bony metastases. In the majority of the trials, however, prostate cancer patients are well represented, comprising more than 20% of the total (Nielsen 1998, 33% prostate cancer[1]; Steenland 1999, 23% prostate cancer[2]; Kirkbride 2000, 23% prostate cancer[3]; Roos 2005, 29% prostate cancer[4]; Hartsell 2005, 50% prostate cancer[5]; Bone pain Trial Working Party 1999, 34% prostate cancer[6]). When results for prostate cancer subgroups were available they did not differ from those of the entire cohort.[2] [7] Trials were not blinded and thus were assessed as low quality.

The role of local radiotherapy in the management of uncomplicated bone pain is well established. It is considered a standard therapy for painful bone metastases with published accounts of its efficacy dating back to the 1920s. As such, RCTs comparing radiotherapy with no therapy would be considered unethical. An indirect way to consider the efficacy of radiotherapy for the treatment of metastatic bone pain is to examine the effects of lowering radiation doses. Poorer outcomes at lower doses would support the notion that radiotherapy is an effective treatment of metastatic bone pain. This review does not address the issue of the optimal fractionation schedule for multiple fractions.

Overall response rates of around 65–80 % and complete response rates of around 10–50% may be achieved as seen in the studies by Steenland et al.[2][8] Rates vary with the definition of pain response, period after treatment assessed and the percentage of patients lost to follow-up or for whom data are missing.

Low dose comparisons

Two randomised controlled trials (Hoskin 1992, n=270, 13% prostate cancer patients[9]; Jeremic 1998, n=219, 17% prostate cancer patients[7]) showed that overall pain responses were significantly ($P<0.01$ and $P=0.002$) worse when patients were treated with a single dose of 4Gy rather than 8Gy.

Single versus multi-fraction regimens (differing doses)

The main issue at hand has been the relative efficacy of various fractionation schedules in effecting pain relief. Nine RCTs compared a single fraction of 8Gy with multiple fractions ranging from 20Gy in five fractions to 30Gy in ten fractions. One of these trials[4] examined the effect of different fractionation schedules for the treatment of neuropathic bone pain in particular.

Pain endpoints and patient survival rates varied and the periods assessed ranged from four weeks postradiotherapy to twelve months post-radiotherapy. Complete response is generally defined as resolution of pain relief without need for analgesic consumption; partial response is defined as pain reduction of 2 or more at the treated site on a 0–10 scale without analgesic increase, or analgesic reduction of 25% or more from baseline without an increase in pain.[10] However, other integrated painanalgesia response systems exist.[3][4][5][8] In any study, however, integrated pain-analgesic response estimates may be diluted by pain from symptomatic metastases outside of the irradiated area.

Two of these trials assessed less than 100 patients[11][12] and thus in these studies an absence of a significant difference in response rates may not reflect equivalence but rather a failure to detect a difference. Two trials were designed to detect a difference in response rate greater than 15% (Nielsen 1998, n=24152; Bone Pain Trial Working Party 1999, n=76157), one trial was designed to detect a difference in response rate greater than 18% (Roos 2005, n=27255), and one trial was designed to detect a difference in response rate greater than 10% (Steenland 1999, n=115753).

Despite these differences, all nine trials were unable to detect any significant difference in overall pain response, whether crude or actuarial response rates, and in the three studies that examined duration of response no significant differences were seen. Prognostically favourable patients with longer life expectancy did not derive greater benefit from multi-fraction schedules.[8][13]

Whilst these trials found that a single fraction was not significantly worse than a higher-dose multifraction regimen in terms of initial pain response, the question as to whether they were equivalent was rarely addressed. In the trial reported by Roos[4], treatments were to be considered equivalent if the 90% confidence interval for the difference in risk ratios was greater than 15%. In this trial, pain palliation with single fraction radiotherapy was not a statistically worse treatment group, however they were unable to show that it was equivalent to the higher-dose multi-fraction regimen.

Seven trials were unable to detect any significant difference in complete response. The trial reported by Hartsell 2005 (n=573)[5] was designed to detect greater than 21.7% change in complete pain relief. However it is unclear whether the other trials were sufficiently powered to detect a difference.

Seven of these trials reported re-treatment rates. Re-treatment rates at the physician's discretion were higher (8–18%) in the single-dose arm in four of the seven trials examining re-treatment rates (Price 1986, n=288, p=0.006[14]; Bone Pain Trial Working Party 1999, p<0.001[6]; Steenland 1999, p<0.001[2]; Hartsell 2005, p<0.001)[5]. These studies were not blinded and re-treatment may be subject to bias in the same way that initial pain response may be subject to bias.

Single fraction treatment did not have an adverse impact on quality of life[1][2] [5][11][15] or significantly increase the incidence of spinal cord compression at the index site.[4][6] Five studies examined the incidence of pathological fractures at the index site. Two studies found no difference in the incidence of pathological fractures [4][5] whereas the larger Steenland study[2] found a significant (p<0.05) increase in the incidence of pathological fractures within the single fraction treatment group. No significant difference was found in the incidence of femur fractures[14] or long bone fractures[6]

Eight trials examined acute toxicity.[1][2] [4][5][6], [11][12][14] There were no statistically significant increases in short-term adverse outcomes with single-dose radiotherapy other than for the flare (p=0.03, Roos 200555). In one study, more severe toxicity (grade 2–4) was significantly decreased in the single fraction arm (p = 0.02, Hartsell 2005).56

These results support the conclusion that there is no evidence to suggest any dose response for initial pain response rates when comparing a single fraction of 8Gy versus multiple fractions ranging from 20Gy/5f to 30Gy /10f. That is, single fraction of 8Gy is not worse than a course of multi-fraction treatment for the endpoint of initial pain response. This is in agreement with the meta-analysis by Sze et al[16] and updated,[17] which included additional trials that did not meet the inclusion criteria for these guidelines.

Greater patient convenience and lower cost may make single fractions an attractive option for treatment even at the expense of higher re-treatment and fracture rates. However, two studies demonstrated that a significant proportion of patients may prefer multiple fractions if that will result in lower re-treatment and fracture rates.[18] [19]

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7.2.7.2 Evidence summary and recommendations

Evidence summary	Level	References
Low-dose external beam radiotherapy There are no controlled trials comparing EBRT with no treatment. As EBRT is a recognised treatment of metastatic bone pain, RCTs comparing radiotherapy with no therapy would be considered unethical. Poorer outcomes at lower doses support the notion that EBRT is an effective treatment of metastatic bone pain.	II	[7], [9]
Single versus multi-fraction higher-dose EBRT No dose response exists for pain response rates when comparing a single fraction of 8Gy versus multiple fractions ranging from 20Gy/5f to 30Gy/10f. That is, a single fraction of 8Gy is not worse than a course of multi-fraction treatment for the endpoint of pain response. Fracture rates following radiation are low (<5%). There is no consistent evidence that fracture rates or spinal cord compression rates are higher in single fractions. Single fractions are associated with a higher re-treatment rate.	II	[1], [2], [3], [4], [5], [6], [8], [11], [12], [14], [15]

Evidence-based recommendation	Grade
Radiotherapy is an effective and well-tolerated treatment for metastatic bone pain. A single dose of 8Gy is as effective as higher fractionated doses (eg 20–30Gy) in reducing bone pain. The higher incidence of re-treatment with lower-dose single fraction regimens should be considered as part of the decision-making process.	**C**

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7.2.7.3 References

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7.2.8 Radiotherapy treatment of loco-regionally progressive disease

Contents

7.2.8.1 What is the evidence for the effect of radiotherapy in palliation of soft tissue disease of EBRT to the prostate for symptom treatment in locally advanced disease and to local metastases (such as the lymph nodes for symptom treatment such as lymphoedema and painful lymph nodes)?

The vast majority of patients with hormone-resistant prostatic carcinoma present with symptomatic bony metastases as their major symptom. There is a subset of patients, however, who present with significant pelvic symptoms (obstructive urinary symptoms, bleeding, rectal obstruction, pelvic and rectal pain) relating to locally progressive disease with or without symptomatic bony disease. The median survival of these men with small-volume distant disease can be around 18–24 months and 6–12 months in those with more extensive disease. The optimal management of these patients remains far from clear. There are no randomised studies addressing the role of pelvic radiotherapy. However a number of retrospective studies suggest that a fractionated course of high-dose palliative pelvic radiation treatment can be extremely useful in obtaining growth restraint and alleviating the symptoms arising from the disease process.[1][2][3][4][5][6][7][8][9] Bleeding (haematuria) responds particularly well. Similar results were found in a more recent case series.[10]

A small subset of patients can also present with significant metastatic nodal disease within the pelvis, abdomen, chest and supraclavicular or lower neck region. The enlarged nodes can result in significant pain or obstructive symptoms due to the extrinsic compression on the adjacent organs. No randomised or retrospective studies have specifically addressed the role of radiation treatment in this setting. It is unlikely that any such studies will be undertaken.

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7.2.8.2 Evidence summary and recommendations

Evidence summary	Level	References
Although there are no randomised prospective trials to address whether radiotherapy has a beneficial effect on incurable prostate cancer and its soft tissue metastases, the question of benefit remains clinically important. Therefore, nine case series have been reviewed noting that these all pertain to locally advanced prostate cancer. There were no significant publications reviewing soft tissue metastases.	IV	[1], [2], [3], [4], [5], [6], [7], [8], [9]

Evidence-based recommendation	Grade
Radiotherapy can be considered for palliation of symptoms secondary to locally progressive	**D**

Evidence-based recommendation	Grade
disease.	

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7.2.8.3 References

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7.2.9 Radiotherapy alone for spinal cord compression

Contents

7.2.9.1 What is the benefit of EBRT alone given for malignant spinal cord compression?

Spinal cord compression/nerve root compression (with or without surgery)

Spinal cord compression is an oncological emergency. It is a potentially devastating complication of metastatic prostate cancer that can result in pain, paraplegia, incontinence and loss of independence. It is not uncommon for sequelae of metastatic disease to occur in between 1% and 12% of patients.[1] No randomised controlled trials were found that examined treatments for spinal cord compression specifically for prostate cancer patients. Therefore, the systematic reviews were broadened to cover any trials that included prostate cancer patients.

Radiotherapy is an effective and well-tolerated treatment for metastatic bone pain. It has been the cornerstone of management for malignant spinal cord compression (MSCC) for decades as it is a noninvasive approach and associated with relatively low toxicity. Its effectiveness is based largely on retrospective outcomes from single institution series. There are no randomised trials comparing radiotherapy alone with either surgery alone or dexamethasone alone for malignant spinal cord compression. There is one randomised trial of 276 patients comparing two fractionation schedules (16Gy/2f vs 30Gy/8f) that gives outcome data of radiation alone.[2] In this trial only 14% of the entire cohort were prostate patients.

The Maranzano[2] trial confirms the importance of radiotherapy in the management of spinal cord compression, with 90% of ambulatory patients still walking at one month and 28% of non-ambulatory patients regaining ability to walk.[2] However, regaining ambulation if paraplegic is rare. More thanhalf of patients experienced pain relief but overall survival was poor, with median survival of four months. Although no significant differences in the fractionation schedules were seen, clinically significant differences could not be excluded. One-year survival was 18% for the longer fractionation versus 10% with the shorter approach. Five (versus none) infield recurrences were seen in the shorter fractionation group.

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7.2.9.2 Evidence summary and recommendations

Evidence summary	Level	References
There are no randomised trials comparing radiotherapy with either surgery or dexamethasone alone for spinal cord compression. There is one randomised trial comparing two different fractionation schedules for unfavourable risk malignant spinal cord compression. It demonstrated no significant differences between the schedules, though clinically important differences cannot be excluded	II	[2]

Evidence-based recommendation	Grade
For patients with malignant spinal cord compression the use of radiation is recommended. The optimal fractionation schedule of radiotherapy is unknown.	**D**

Evidence-based recommendation	Grade
Patients being treated with radiation for spinal cord compression should be given dexamethasone at time of diagnosis.	**B**

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7.2.9.3 References

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7.2.10 Surgery in malignant spinal cord compression

Contents

7.2.10.1 What is the role of surgery in the treatment of malignant spinal cord compression?

The role for surgery has long been controversial in malignant spinal cord compression from metastatic prostate cancer. It is acknowledged that the outcomes with radiotherapy alone are suboptimal, especially if patients are non-ambulatory or paraplegic at presentation. However, clinicians had concerns subjecting patients who are often unwell with a poor median survival to the rigors of surgery for a non-quantifiable degree of benefit. Also, it was not known whether surgery should consist of a decompression laminectomy alone (to relieve pressure on the spinal cord) or the more aggressive circumferential decompression laminectomy where the entire affected vertebrae is removed. Decompressive laminectomy should be considered when radiotherapy cannot be given due to previous treatment or progression during or shortly after radiotherapy.

There are only two randomised trials comparing surgery with radiotherapy versus radiotherapy alone.[1][2]The Patchell study of 101 patients (16% with prostate cancer) compared radiotherapy alone with direct circumferential decompression (with spinal stabilisation if spinal instability present) followed by radiotherapy.

The Patchell study demonstrated a clinically significant improvement with the addition of aggressive surgery to radiation only and was stopped early as it met pre-set termination criteria. For ambulatory patients at presentation, 94% versus 74% were walking post-treatment in the surgery and radiotherapy arms respectively. For non-ambulatory patients, the rates were 62% versus 19%. There was a median survival improvement of 126 versus 100 days (p=0.03) and a significant improvement in pain levels as judged by median mean daily morphine doses (p=0.002) with surgery.

Patients have to be carefully selected for the aggressive approach outlined in the Patchell study. They need to be fit for aggressive surgery, have a life expectancy of more than three months, have a single site of cord compression, have neurologic symptoms present, and have surgery within 48 hours if paraplegic. To be considered for this approach, hospitals would need adequate neurosurgical services and appropriate supportive care. This is likely to be available only in major teaching hospitals. The role of aggressive surgery for early malignant spinal cord compression seen on imaging but not causing neurologic symptoms is unclear.

The Young study of 29 patients (14% had prostate cancer) compared radiotherapy alone with laminectomy plus radiotherapy. This underpowered study demonstrated no benefit in ambulation or bladder function with the addition of a decompression laminectomy to radiotherapy. The Young study differed from the Patchell study in having significantly less aggressive surgery.

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7.2.10.2 Evidence summary and recommendations

Evidence summary	Level	References
There is one randomised trial demonstrating a significant clinical benefit with the addition of aggressive surgery (direct circumferential decompression) to radiotherapy for appropriate patients with symptomatic malignant spinal cord compression	II	[1]
The role of decompression laminectomy prior to radiotherapy is unknown, with one small trial demonstrating no benefit.	II	[2]

Evidence-based recommendation	Grade
For highly selected patients with malignant spinal cord compression, vertebrectomy with spinal stabilisation prior to radiotherapy should be considered. The role of decompression laminectomy prior to radiotherapy is unknown.	**C**

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7.2.10.3 References

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7.2.11 Steroids for malignant spinal cord compression

Contents

7.2.11.1 What is the efficacy of steroids for the treatment of malignant spinal cord compression?

Steroids such as dexamethasone are commonly utilised for patients with malignant spinal cord compression, often in conjunction with radiotherapy. They are thought to decrease oedema and thus prevent further impediment of blood supply. An anti-tumour effect in some cases may also play a role. Transient reductions in pain and improvement in neurologic function are well recognised with steroids alone. However, the absolute degree of benefit when combining steroids with radiotherapy is unknown and the recommended dosages are controversial.

There are three small low-quality randomised controlled trials evaluating the efficacy of steroids for malignant spinal cord compression. The Sorensen 1994 study[1] randomised 57 patients to receive high-dose dexamethasone (96mg initial bolus) combined with radiotherapy versus no dexamethasone and radiotherapy. Two trials compared the effects of different doses of dexamethasone as an adjuvant to radiotherapy[2][3] The

Vecht 1989 trial randomised 37 patients to an initial dose of either 100mg or 10mg of dexamethasone in addition to radiotherapy.[3] The Graham 2006 trial[2] randomised 20 patients to an initial dose of either 96mg or 16mg dexamethasone combined with radiotherapy but was terminated prematurely because of poor accrual.[2] These studies included only a small (9%) or unspecified percentage of prostate patients and had wide variety of clinical presentations and imaging performed.

Even with small numbers, the Sorensen paper[1] demonstrated the importance of dexamethasone for malignant spinal cord compression, with 59% of those treated with dexamethasone (96mg initialbolus) in addition to radiotherapy ambulant at six months compared with 33% of those treated with radiotherapy alone (p=0.05). The addition of dexamethasone significantly (p=0.046) improved the probability of surviving with gait function in the year following treatment without a significant increase in serious toxicities. The Vecht trial comparing high and low doses of dexamethasone showed no difference in pain, ambulation rates or bladder function between the two arms but the low power of the study (37 patients) cannot exclude clinically important differences.

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7.2.11.2 Evidence summary and recommendations

Evidence summary	Level	References
There is one small trial of high-dose dexamethasone and radiotherapy versus radiotherapy alone. This demonstrated a significant improvement in ambulation rates in the steroid arm.	II	[1]
The optimal dose of steroids is unknown, with one small trial demonstrating no significant difference in efficacy of higher-dose dexamethasone over lower doses.	II	[3]

Evidence-based recommendation	Grade
Patients being treated with radiotherapy for malignant spinal cord compression should also receive dexamethasone.	**C**

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7.2.11.3 References

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7.2.11.4 Appendices

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7.2.12 Hemibody external beam radiotherapy

Contents

7.2.12.1 What is the efficacy of Hemibody (widefield) external beam radiotherapy in the palliation of uncomplicated bone pain?

Hemibody radiotherapy refers to the practice of irradiation of either the lower body half (pelvis and legs) or the upper body half (upper lumbar spine, chest, arms with or without the skull). It was a commonly used treatment for prostate cancer with multifocal pain when effective chemotherapy or radionucleide therapy was not available.

There are no controlled trials comparing pain responses with and without hemibody radiotherapy.

One low-quality RCT (Poulter 1992, n=499, 33% prostate cancer patients[1]) examined whether hemibody radiation in addition to local radiation retarded disease progression for patients with moderately to severely painful single or multiple bone metastases. The addition of hemibody radiation (8Gy, single fraction) to local radiotherapy significantly retarded disease progression as evidenced by increase in lesion size (p=0.03) and number (p=0.01). However, in this study[1], hemibody radiation was associated with a significant increase in grades 3 and 4 haematological toxicity (p=0.004), with leukopenia being significantly worse (p=0.01).

A quasi-randomised controlled trial by Scarantino (n=144, 70% prostate cancer)[2] examined the effects of increasing the dose of hemibody irradiation in conjunction with local radiotherapy on progression and toxicity. This study was unable to show that increasing multi-fraction hemibody radiation dose from 10Gy to 20Gy significantly reduced the development of new metastases when given in conjunction with local radiotherapy.

A second low-quality RCT by Salazar 2001 (n=156, 32% prostate cancer)[3] examined escalating doses of hemibody radiotherapy without local radiotherapy. When given alone, increasing hemibody radiation dose as multi-fraction regimens from 8Gy to 15Gy[3] did not significantly improve overall pain responses (response rates 89% and 92%). However, it did significantly (p=0.016) improve complete pain responses without an apparent increase in grade 3–4 toxicity (16% at 8Gy and 8% at 15Gy).

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7.2.12.2 Evidence summary and recommendations

Evidence summary	Level	References
There are no controlled trials comparing pain responses with and without hemibody radiotherapy.	II	[1], [3]
Increasing hemibody radiation doses above 8Gy does not improve overall pain palliation. There is no good evidence to support the use of fractionated hemibody irradiation over a single fraction. Adding hemibody radiation to local external beam radiotherapy while retarding progression increases grade 3–4 haematological toxicity.	III-1	[2]

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7.2.12.3 References

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7.3 Bisphosphonates

Bisphosphonates

No recommendations have been made for hormone naïve metastatic disease. See *What is the evidence for the use of bisphosphonates in the prevention of skeletal events?* for a discussion of a single trial of bisphononates for hormone-naïve metastatic bone disease.

7.4 Chemotherapy

See Emerging therapies for ongoing trials in this area.

8 Castration-resistant prostate cancer

8.1 Castration-resistant prostate cancer

Defining castrate-resistant prostate cancer has been a matter of much consideration due to:

- the heterogenous manifestations of prostate cancer progression, and
- the fact some patients who progress with a castrate-level of testosterone respond to second-line hormone manipulations.

Therefore a consensus statement has been developed by the Prostate Cancer Clinical Trials Working Group on what defines progression to ensure standard entry criteria onto a clinical trial.[1] This in turn provides guidance to physicians treating patients outside a clinical trial. Castrate-resistant prostate cancer is defined as progressive disease despite castrate levels of testosterone. Progression can be deemed to have occurred based on changes in PSA and/or increase of measurable disease and/or increasing burden of disease on bone scan, while controlling for antiandrogen withdrawal responses. These criteria are standardised by assessments and include:

- *PSA*. Obtain sequence of rising values at a minimum of one-week intervals. If the patient is being deemed to have progressed by PSA alone then 2.0ng/mL must be the minimum starting value. The baseline value (#1) is the last PSA measured before increases are documented, with subsequent values obtained a minimum of one week apart. If the PSA at time point 3 is greater than that at point 2, and point 2 was greater than point 1, then PSA documented progression has been met. If the PSA at point 3 is not greater than point 2, but value at point 4 is, the patient has documented progression.
- *Progression of measurable disease.* Whether progression of measurable disease (such as nodal or visceral progression) is the same as the RECIST definition (target and non-target). Increasing soft tissue castrate-resistant prostate cancer can occur in the absence of a rising or even detectable PSA. Only lymph nodes greater than or equal to 2cm in diameter should be used to assess changes in size.
- *Progression of disease in the prostate/ prostate bed (primary site).* This should be considered. To document presence or absence of disease, all documentation of prior treatment of primary tumour is required, as are evaluations such as directed pelvic imaging (CT, MRI, positron emission tomography (PET)/CT, endorectal MRI, transrectal ultrasound). Clinical progression can be manifest by bladder outlet obstruction and/or disease extension into the bladder with ureteric obstruction.
- *Bone-scan progression.* This is defined as appearance of two or more new lesions. Ambiguous results may require confirmation by other imaging modalities (e.g. CT or MRI). Symptomatic progression of an isolated lesion with a castrate level of prostate cancer would also qualify as progressive disease.

Other sites of disease can also be evidence of prostate cancer progression, such as worsening epidural lesions. Radiographic and/or clinical documentation of disease in these sites would also qualify as progression.

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8.1.1 Clinical questions

- Is any one hormone therapy (androgen ablation) superior to another when given in the second-line settir (after relapse from first-line androgen ablation) in terms of response, progression-free survival or surviva
- Should LHRH agonist be continued when the patient is hormone refractory?

Guidelines:Prostate_cancer/Management/Locally_advanced_and_metastatic /Bisphosphonates|Bisphosphonates]]

- What is the evidence for the use of bisphosphonates in the prevention of skeletal events?

- What is the evidence for the use of bisphosphonates in the treatment of bone pain?

Radioisotopes

- What is the effectiveness of unsealed radioisotopes in the management of bone pain from prostate canc
- Do unsealed radioisotopes improve survival in metastatic prostate cancer?
- What is the evidence that quality of life is improved with unsealed radioisotopes in prostate cancer?
- What is the toxicity of unsealed radioisotopes for treatment of metastatic prostate cancer?

Chemotherapy

- Does cytotoxic chemotherapy give a survival benefit or any other benefits in terms of quality of life improvement, control of pain or other symptoms compared to patients not receiving chemotherapy or receiving different types of chemotherapy?

Chemotherapy-related clinical questions, for which no evidence was found:

- Clinical question:Is there any benefit derived from chemotherapy for patients who do not have any symptoms from the prostate cancer (asymptomatic)?
- Clinical question:Is there any benefit derived from chemotherapy for patients who are not hormone refractory comparing chemotherapy plus hormone therapy with hormone therapy alone?
- Clinical question:Has the effectiveness of chemotherapy been compared to external beam radiotherapy radio-isotopes (strontium or samarium) in a randomised study?
- Clinical question:Can radio-isotopes (strontium or samarium) be used at the same time as (simultaneous with) chemotherapy (combined therapy) without excessive toxicity?

8.2 References

1. ↑ Prostate Cancer Clinical Trials Working Group, Scher HI, Halabi S, Tannock I, Morris M, Sternberg CN, et al. *Design and end points of clinical trials for patients with progressive prostate cancer and castrate levels of testosterone: recommendations of the Prostate Cancer Clinical Trials Working Group.* J Clin Oncol 2008 Mar 1;26(7):1148-59 Available from: http://www.ncbi.nlm.nih.gov/pubmed/18309951.

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8.1 Introduction

8.1.1 Castration-resistant prostate cancer

Defining castrate-resistant prostate cancer has been a matter of much consideration due to:

- the heterogenous manifestations of prostate cancer progression, and
- the fact some patients who progress with a castrate-level of testosterone respond to second-line hormone manipulations.

Therefore a consensus statement has been developed by the Prostate Cancer Clinical Trials Working Group on what defines progression to ensure standard entry criteria onto a clinical trial.[1] This in turn provides guidance to physicians treating patients outside a clinical trial. Castrate-resistant prostate cancer is defined as progressive disease despite castrate levels of testosterone. Progression can be deemed to have occurred based on changes in PSA and/or increase of measurable disease and/or increasing burden of disease on bone scan, while controlling for antiandrogen withdrawal responses. These criteria are standardised by assessments and include:

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- *Progression of disease in the prostate/ prostate bed (primary site).* This should be considered. To document presence or absence of disease, all documentation of prior treatment of primary tumour is required, as are evaluations such as directed pelvic imaging (CT, MRI, positron emission tomography (PET)/CT, endorectal MRI, transrectal ultrasound). Clinical progression can be manifest by bladder outlet obstruction and/or disease extension into the bladder with ureteric obstruction.
- *Bone-scan progression.* This is defined as appearance of two or more new lesions. Ambiguous results may require confirmation by other imaging modalities (e.g. CT or MRI). Symptomatic progression of an isolated lesion with a castrate level of prostate cancer would also qualify as progressive disease.

Other sites of disease can also be evidence of prostate cancer progression, such as worsening epidural lesions. Radiographic and/or clinical documentation of disease in these sites would also qualify as progression.

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- Clinical question:Has the effectiveness of chemotherapy been compared to external beam radiotherapy radio-isotopes (strontium or samarium) in a randomised study?
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1. ↑ Prostate Cancer Clinical Trials Working Group, Scher HI, Halabi S, Tannock I, Morris M, Sternberg CN, et al. *Design and end points of clinical trials for patients with progressive prostate cancer and castrate levels of testosterone: recommendations of the Prostate Cancer Clinical Trials Working Group.* J Clin Oncol 2008 Mar 1;26(7):1148-59 Available from: http://www.ncbi.nlm.nih.gov/pubmed/18309951.

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8.2 Second- line hormonal manipulation

Contents

8.2.1 Is any one hormone therapy (androgen ablation) superior to another when given in the first line setting in terms of survival in metastatic disease?

Once a patient's cancer has started to grow again or recur with a castrate level of testosterone, he enters another stage, called castrate-resistant prostate cancer. However, despite the fact the cancer is growing with a castrate level of testosterone (e.g. less 50ng/dL), there are some cancers that respond to further hormone manipulations. This has been attributed to a number of mechanisms including (i) upregulation of the androgen receptor and low circulating levels of androgen and (ii) intratumoralproduction of androgens which drive cancer growth.

There have been twelve small- to medium-sized randomised clinical studies assessing a variety of second-line hormone manipulations. Although the studies are numerous, the amount of meaningful data is limited. This is due to the small size of many of the studies introducing a significant risk of a bias, differing primary hormone therapies and manipulations. Interventions included institution of non-steroidal anti-androgens if not already being taken[1]; comparisons of anti-androgens with low-dose corticosteroids[2][3] and oestrogens[4][5] comparisons of megesterol acetate with oestrogens[6] and corticosteroids[7]; high-dose oestrogens[8]; medroxyprogesterone acetate[9]; and adrenal androgen suppression with agents like ketoconazole (with hydrocortisone).[10]

No second-line hormone manipulation has clearly been shown in a randomised controlled trial (RCT) to lead to an improvement in overall survival. It is unknown whether this is because this strategy is not effective in enough people to affect the overall survival of the population or because of the paucity of well-powered trials to answer this question. It is well demonstrated that a minority of patients will have some evidence of prolonged (greater than 12 months) disease control as evidenced by reduction in symptoms and/or PSA declines and rarely,

changes in radiographic evidence of disease.[4][10] For patients who had previously undergone castration only, there was no significant difference between the response rates for anti-androgens and prednisone or diethylstilbestrol.[2][3][4] For patients who had had failed combined androgen deprivation, there were significant clinical and/or biochemical improvements with changing the anti-androgen[1] and, when anti-androgens were withdrawn, with ketoconazole and hydrocortisone.[10] There are no RCTs comparing ketoconazole with other secondline hormone therapies.

There are no RCTs examining the effects of androgen withdrawal. Case series have shown that for a subgroup of patients who have progressed on combined androgen deprivation, withdrawal of the antiandrogen can cause a decline in PSA levels.[10][11][12] In one of the larger and more recent series 11% of patients who stopped anti-androgen (flutamide, bicalutamide or nilutamide) therapy had a PSA decrease > 50% which lasted a median of 5.9 months. [10]

The lack of clear-cut data guiding therapy for this patient population is problematic because most patients with metastatic prostate cancer progress on androgen deprivation and any response from altering hormonal therapy regimens is short-lived for most patients with our current agents. As such, findings from studies in this setting are relevant to a large patient population. Guidance and availability of agents to treat this patient population is a significant clinical need, as once progression is demonstrated, the patients have a relatively short life expectancy. All of the agents listed above have a manageable side-effect profile and would favour trialling a hormone manipulation, especially in patients with no or minimal symptoms. This approach will not inappropriately defer the institution of chemotherapy, which will be used when a patient has progressed, and the manoeuvre possibly results in significantly delaying the use of chemotherapy in a minority of patients.

The agents that can be employed as second-line hormone manipulations are generally available in Australia and have a mild side-effect profile which makes it feasible to trial these in most patients. The one caveat is ketoconazole, which, when used in high doses (400mg tds) can cause some significant adverse events.[10]This can be minimised by close monitoring of liver function tests and starting with 200mg tds with replacement doses of hydrocortisone and escalate as tolerated. Antiandrogens and low-dose corticosteroids are available on the PBS for metastatic prostate cancer. Ketoconazole however is not available and costs approximately $150 per month unless it is on a hospital formulary for this indication. Only one RCT examined quality of life outcomes using a validated instrument, the EORTC-C30 instrument. In that study overall quality of life scores, pain scores and gastrointestinal symptom scores were significantly better with prednisone as compare with flutamide over 24 weeks.[2]

To help put the prior data in the context of current drug availability, one has to consider the following. With the emergence of chemotherapy and/or stage migration and/or improved supportive cancer care, the median overall survival for patients with castrate-resistant prostate cancer is now 18 months from the start of chemotherapy.[13] It is of note that the median overall survival is detailed to be about 12 months from institution of second-line hormone manipulation in the studies listed. These studies were done prior to the demonstrated benefit of docetaxel for patients with castrate-resistant prostate cancer. Specifically, prior studies have shown mitoxantrone plus prednisone was associated with a better palliative response than the prednisone (low-dose corticosteroid) alone. It is also of note that in the pivotal docetaxel plus prednisone versus mitoxantrone plus prednisone studies[13], patients had a median of four previous hormone manipulations, indicating common use of hormone manipulations prior to trialling chemotherapy. It is of relevance to point out the ‘clock’ for the median overall survival of about 18.5 months for docetaxel and 16.4 months for mitoxantrone

started from when the chemotherapy was given (ie after the hormone manipulations). It is also worth noting that more recently, agents which (i) block the formation of testosterone from cholesterol by inhibiting an enzyme known as 17-hydroxylase/17,20 lyase (abiraterone), and (ii) are more potent antagonists of the androgen receptor, have been shown to cause disease regression as single agents in the postchemotherapy setting. These agents are being assessed in patients with castrate-resistant disease (for example the NCT00638690 or COU-AA-301 trial of abiraterone acetate). These are well-powered studies and will provide important information about the utility of second-line hormone manipulations in patients with castrate disease.

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8.2.2 Evidence summary and recommendations

Evidence summary	Level	References
Data from large randomised studies are limited. No second-line hormone manipulation in an RCT has been clearly shown to lead to an improvement in overall survival. A minority of patients have prolonged disease control with further hormone manipulations such as an anti-androgen or adrenal androgen suppression with ketoconazole and hydrocortisone In one RCT, overall quality of life scores, pain scores and gastrointestinal symptom scores were significantly better with prednisone compared with flutamide.	II	[1], [2], [3], [4], [5], [6], [7], [8], [9], [10], [14], [15], [16]

When assessing the data in total and in the context of the role of docetaxel (active chemotherapy), are recommendation of a course of action can be made for patients with evidence of progression on androgen deprivation.

Evidence-based recommendation	Grade
There is a sequence of actions that should be followed when a patient is shown to have progressive cancer on androgen deprivation therapy. First, confirm that the patient has a castrate level of testosterone if on an LHRH agonist therapy. If the patient is also on a nonsteroidal anti-androgen, this agent could be withdrawn and observed for the possibility of an anti-androgen withdrawal phenomenon. It is reasonable to trial further hormone manipulations if the patient is asymptomatic or minimally symptomatic prior to use of chemotherapy (e.g. docetaxel).	**C**

Bisphosphonates, radiotherapy and chemotherapy will need to be integrated at some time into overall treatment regimens at this stage of the disease.

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8.2.4 Appendices

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8.3 LHRH agonists when the patient is hormone refractory

Contents

8.3.1 Should LHRH agonist be continued when the patient is hormone refractory?

An important yet unanswered question is whether a patient should continue LHRH agonist therapy once his disease has progressed while on androgen deprivation. The continued castrate state could also needlessly expose a patient to the adverse events of having lowered testosterone. In addition, a significant portion of men who have been medically castrated do not have recovery of their testosterone once the LHRH agonist is stopped, and are thus being dosed with a drug redundantly. Finally, as the cost of this class of drugs is significant, cost-effectiveness is also important. (Obviously, this question does not pertain to patients who have undergone a surgical castration).

There are no RCTs addressing this question. There are two retrospective reviews that analysed two unique datasets and assessed the outcome of patients who did and did not maintain their castrate state when treated with chemotherapy in the pre-docetaxel era. In essence, one study suggested a benefit[1] and the other did not suggest a benefit.[2] At most, we can suspect that continuing the LHRH agonist does not worsen a patient's prognosis. If, however, a patient is having significant adverse events from maintaining a castrate state (hot flushes, depression, weight gain) it is reasonable to hold the LHRH dosing. However, it should be recognised that some patients have a rapid recurrence of their testosterone and anecdotally more rapid recurrence of their cancer and respond to re-instituting a castrate state. Moreover, it is contended that based on the molecular biology of prostate cancer, it is intuitive that avoiding physiological androgen level (ie growth factor) availability to cancer cells will possibly still retard tumour progression versus return of physiological levels of testosterone.

In accordance with the design of the trials that have led to the survival advantage for docetaxel in castrate-resistant prostate cancer[3][4] the arguments appear to favour continuation of the LHRH agonist agent. Another tenuous reason for maintaining a castrate state can be derived from the activity of second-line hormone manipulations, with the amount of benefit–if there is one–to be defined by the continuing large phase 3 trials of the newer agents such as abiraterone. Specifically, this observation details the sensitivity of some cancer cells to androgens even when growing in a castrate environment. However, it is unknown whether these newer agents require a castrate state for maximum benefit.

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8.3.2 Evidence summary and recommendations

Evidence-based recommendation
There is insufficient evidence to make a recommendation as to whether a patient should continue LHRH agonist therapy once his disease has progressed while on androgen deprivation.

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8.3.3 References

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8.4 Bisphosphonates

8.4.1 Bisphosphonates

Bone is the most frequent site for metastases from prostate cancer. It has been estimated that 85% of men with advanced prostate cancer, particularly when the disease is not controlled by androgen deprivation therapy, will have bony metastases. These metastases lead to bone pain, pathological fractures, spinal cord compression and in rare instances, disturbances in serum calcium levels sufficient to produce symptoms. This composite of bone complications associated with cancer has been encompassed by the term ‘skeletal related events’ (SRE). Bisphosphonates have been shown to be effective in reducing the incidence of SREs in myeloma and breast cancer.[1][2][3]

Although prostate cancer usually results in sclerotic or osteoblastic lesions, there is evidence of the presence of an osteolytic component and this may be inhibited by bisphosphonates.[4][5][6][7]

This section examines the evidence for the use of bisphosphonates in the prevention of SRE and bone pain control in men with metastatic prostate cancer.

There are two points regarding bisphosphonates and prostate cancer worth clarifying. First, the use of bisphosphonates to prevent prostate cancer associated SREs is distinct from discussions about the management of osteoporosis induced by therapies used to treat prostate cancer. Namely, androgen deprivation can lead to a decrease in bone mineral density and in some cases, osteoporotic crush fractures. The relevance of this is paramount in the adjuvant setting, and the dosing and schedules of bisphosphonates are far lower than the doses for prevention of SREs. This matter is not addressed in this review. The second point to appreciate when reviewing the following dataset is that bisphosphonates have vastly different potencies. This variability probably leads to the heterogeneity in the outcomes and contributes to the limitations of the recommendations based on the current dataset.

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8.4.1 Bisphosphonates

8.4.1.1 Bisphosphonates

Bone is the most frequent site for metastases from prostate cancer. It has been estimated that 85% of men with advanced prostate cancer, particularly when the disease is not controlled by androgen deprivation therapy, will have bony metastases. These metastases lead to bone pain, pathological fractures, spinal cord compression and in rare instances, disturbances in serum calcium levels sufficient to produce symptoms. This composite of bone complications associated with cancer has been encompassed by the term 'skeletal related events' (SRE). Bisphosphonates have been shown to be effective in reducing the incidence of SREs in myeloma and breast cancer.[1][2][3]

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8.4.1.2 References

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8.4.2 Bisphosphonates and the prevention of skeletal related events

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8.4.3 Bisphosphonates in the management of bone pain

Contents

8.4.3.1 What is the evidence for the use of bisphosphonates in the treatment of bone pain?

Castrate-resistant prostate cancer with existing bone pain

Seven low-quality randomised trials (five were double blind) focus on the treatment of existing pain of patients with painful bone metastases. Measurements of pain and pain outcomes varied. In three studies men in both arms received anti-neoplastic therapy. Due to many confounding factors and study limitations, no firm conclusions can be made regarding the ability of bisphosphonates to manage existing bone pain related to prostate cancer.

The two larger and more informative studies are presented below:

Small et al 2003[1] examining two multi-centred randomised placebo controlled trials reported that pamidronate disodium 90mg (iv) administered every three weeks for 27 weeks did not provide any improved palliation of worst (p=0.89) or average (p=0.71) bone pain compared with placebo in menwith bone pain at study entry. At nine weeks the mean decrease in worst pain score on a 0–10 pain scale was 0.86 in the pamidronate arm and 0.69 in the placebo group (p=0.58). No significant difference was seen in the use of radiation for bone pain relief (p=0.88). However a pre-planned subgroup analysis of men with stable or falling analgesia showed at nine weeks (n=121) a 2.13 unit decrease in mean worst pain score on a 0–10 scale in the pamidronate group, which was significantly (p=0.008) larger than the 0.79 unit decrease in the placebo group. Retrospective subgroup analysis for men with moderate rather than mild baseline pain was reported to show a significant reduction in pain (p=0.004) at nine weeks.

Ernst et al 2003[2] using a randomised double blind design (n=227) compared clodronate (1500 mg iv every three weeks) combined with mitoxantrone and prednisone with placebo and mitroxantrone and prednisone. Similar levels of pain control were noted in both arms; 43% experiencing pain improvement in the clodronate arm and 38% experiencing pain improvement in the placebo group (p=0.52). In this study analgesia was considered in determining the pain response. Similar proportions of men required local radiotherapy with over 12 months follow-up; 16% of men in the clodronate arm and 14% of the men in the placebo arm (p=0.85). However, in a subgroup analysis of men with moderate rather than mild baseline pain (n=49), 58% of men receiving clodronate treatment experienced pain palliation whereas only 26% of men receiving placebo experienced pain palliation (odds ratio=4.6, 95% CI=1.3 to 15.5, p=0.04).

For completeness and to appreciate the limitations of the remaining studies, a brief outline follows.

Smith 1989[3] examined the effect of sodium etidronate on the control of bone pain in a small (n=28) double-blind RCT. Men received either sodium etidronate (iv) 7.5 mg/kg/day for three days then orally 2x200mg/day for one month, or placebo. No significant differences were observed between the two groups (p=1.00).

Adami and Mian 1989[4] randomised 13 men with radiographic evidence of bone metastases to treatment with either 300mg of sodium clodronate (iv) daily or placebo for 14 days. It was reported that pain scores measured using a visual analogue scale and analgesic consumption fell in the treated group, but the statistical significance of the difference compared with the placebo group was not reported. In a multi-centre double-blind RCT without any documented chemotherapy, Strang et al 1997[5] treated 55 men with either sodium clodronate 300mg (iv) for three days followed by oral sodium clodronate at a dose of 3200mg daily or placebo for four weeks. They did not find a significant improvement in pain scores between groups at 32 days follow up, however their data suggested that patients with higher initial pain scores (n=20) may have a better response than those with lower scores. This trial was terminated prematurely because of recruitment difficulties and as a result numbers may not have been sufficient to show any statistically significant differences in men with high pain scores.

Elomaa et al 1992[6] and Kylmala et al 1993[7] reported a randomised trial of sodium clodronate 3.2g/day for one month followed by 1.6g/day for a further five months. At one month there was a reduction in pain from baseline in both the control and the clodronate arms. Although the reduction was greater in the treated group, with 28% of men no longer experiencing pain compared with 15% of men in the control arm, the difference was not statistically significant (p=0.26). The probable explanation for this finding (ie pain relief without clodronate in the control group) was that both groups were started on estramustine phosphate 2x280mg per day at the same time as the clodronate. The symptomatic improvement in the control group was almost certainly due to the effect of the extramustine, thus rendering it difficult to determine the true effect of clodronate.

Kylmala et al 1997[8] reported the results of a similar double-blind placebo controlled trial. Fifty-seven men, most of whom had painful bone metastases, began estramustine therapy and were randomised to either clodronate (iv) 300mg a day for five days and then oral clodronate 1.6g/day for 12 months, or placebo. Again, no significant difference was found between the groups, with mean pain scores in the treatment group not significantly improved from those in the control group over the 12 months.

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8.4.3.2 References

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8.4.3.3 Appendices

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8.4.4 Radiotherapy treatment of bone pain

Contents

8.4.4.1 What is the effectiveness of local external beam radiotherapy (EBRT) in the palliation of uncomplicated bone pain?

Treatment of bone pain

No trials specific to prostate cancer were identified. Most trials have accrued patients with any commonly seen malignant diseases associated with bony metastases. In the majority of the trials, however, prostate cancer patients are well represented, comprising more than 20% of the total (Nielsen 1998, 33% prostate cancer[1]; Steenland 1999, 23% prostate cancer[2]; Kirkbride 2000, 23% prostate cancer[3]; Roos 2005, 29% prostate cancer[4]; Hartsell 2005, 50% prostate cancer[5]; Bone pain Trial Working Party 1999, 34% prostate cancer[6]). When results for prostate cancer subgroups were available they did not differ from those of the entire cohort.[2] [7] Trials were not blinded and thus were assessed as low quality.

The role of local radiotherapy in the management of uncomplicated bone pain is well established. It is considered a standard therapy for painful bone metastases with published accounts of its efficacy dating back to the 1920s. As such, RCTs comparing radiotherapy with no therapy would be considered unethical. An indirect way to consider the efficacy of radiotherapy for the treatment of metastatic bone pain is to examine the effects of lowering radiation doses. Poorer outcomes at lower doses would support the notion that radiotherapy is an effective treatment of metastatic bone pain. This review does not address the issue of the optimal fractionation schedule for multiple fractions.

Overall response rates of around 65–80 % and complete response rates of around 10–50% may be achieved as seen in the studies by Steenland et al.[2][8] Rates vary with the definition of pain response, period after treatment assessed and the percentage of patients lost to follow-up or for whom data are missing.

Low dose comparisons

Two randomised controlled trials (Hoskin 1992, n=270, 13% prostate cancer patients[9]; Jeremic 1998, n=219, 17% prostate cancer patients[7]) showed that overall pain responses were significantly ($P<0.01$ and $P=0.002$) worse when patients were treated with a single dose of 4Gy rather than 8Gy.

Single versus multi-fraction regimens (differing doses)

The main issue at hand has been the relative efficacy of various fractionation schedules in effecting pain relief. Nine RCTs compared a single fraction of 8Gy with multiple fractions ranging from 20Gy in five fractions to 30Gy in ten fractions. One of these trials[4] examined the effect of different fractionation schedules for the treatment of neuropathic bone pain in particular.

Pain endpoints and patient survival rates varied and the periods assessed ranged from four weeks postradiotherapy to twelve months post-radiotherapy. Complete response is generally defined as resolution of pain relief without need for analgesic consumption; partial response is defined as pain reduction of 2 or more at the treated site on a 0–10 scale without analgesic increase, or analgesic reduction of 25% or more from baseline without an increase in pain.[10] However, other integrated painanalgesia response systems exist.[3][4][5][8] In any study, however, integrated pain-analgesic response estimates may be diluted by pain from symptomatic metastases outside of the irradiated area.

Two of these trials assessed less than 100 patients[11][12] and thus in these studies an absence of a significant difference in response rates may not reflect equivalence but rather a failure to detect a difference. Two trials were designed to detect a difference in response rate greater than 15% (Nielsen 1998, n=24152; Bone Pain Trial Working Party 1999, n=76157), one trial was designed to detect a difference in response rate greater than 18% (Roos 2005, n=27255), and one trial was designed to detect a difference in response rate greater than 10% (Steenland 1999, n=115753).

Despite these differences, all nine trials were unable to detect any significant difference in overall pain response, whether crude or actuarial response rates, and in the three studies that examined duration of response no significant differences were seen. Prognostically favourable patients with longer life expectancy did not derive greater benefit from multi-fraction schedules.[8][13]

Whilst these trials found that a single fraction was not significantly worse than a higher-dose multifraction regimen in terms of initial pain response, the question as to whether they were equivalent was rarely addressed. In the trial reported by Roos[4], treatments were to be considered equivalent if the 90% confidence interval for the difference in risk ratios was greater than 15%. In this trial, pain palliation with single fraction radiotherapy was not a statistically worse treatment group, however they were unable to show that it was equivalent to the higher-dose multi-fraction regimen.

Seven trials were unable to detect any significant difference in complete response. The trial reported by Hartsell 2005 (n=573)[5] was designed to detect greater than 21.7% change in complete pain relief. However it is unclear whether the other trials were sufficiently powered to detect a difference.

Seven of these trials reported re-treatment rates. Re-treatment rates at the physician's discretion were higher (8–18%) in the single-dose arm in four of the seven trials examining re-treatment rates (Price 1986, n=288, p=0.006[14]; Bone Pain Trial Working Party 1999, p<0.001[6]; Steenland 1999, p<0.001[2]; Hartsell 2005, p<0.001)[5]. These studies were not blinded and re-treatment may be subject to bias in the same way that initial pain response may be subject to bias.

Single fraction treatment did not have an adverse impact on quality of life[1][2] [5][11][15] or significantly increase the incidence of spinal cord compression at the index site.[4][6] Five studies examined the incidence of pathological fractures at the index site. Two studies found no difference in the incidence of pathological fractures [4][5] whereas the larger Steenland study[2] found a significant ($p<0.05$) increase in the incidence of pathological fractures within the single fraction treatment group. No significant difference was found in the incidence of femur fractures[14] or long bone fractures[6]

Eight trials examined acute toxicity.[1][2] [4][5][6], [11][12][14] There were no statistically significant increases in short-term adverse outcomes with single-dose radiotherapy other than for the flare ($p=0.03$, Roos 200555). In one study, more severe toxicity (grade 2–4) was significantly decreased in the single fraction arm ($p = 0.02$, Hartsell 2005).56

These results support the conclusion that there is no evidence to suggest any dose response for initial pain response rates when comparing a single fraction of 8Gy versus multiple fractions ranging from 20Gy/5f to 30Gy /10f. That is, single fraction of 8Gy is not worse than a course of multi-fraction treatment for the endpoint of initial pain response. This is in agreement with the meta-analysis by Sze et al[16] and updated,[17] which included additional trials that did not meet the inclusion criteria for these guidelines.

Greater patient convenience and lower cost may make single fractions an attractive option for treatment even at the expense of higher re-treatment and fracture rates. However, two studies demonstrated that a significant proportion of patients may prefer multiple fractions if that will result in lower re-treatment and fracture rates.[18] [19]

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8.4.4.2 Evidence summary and recommendations

Evidence summary	Level	References
Low-dose external beam radiotherapy There are no controlled trials comparing EBRT with no treatment. As EBRT is a recognised treatment of metastatic bone pain, RCTs comparing radiotherapy with no therapy would be considered unethical. Poorer outcomes at lower doses support the notion that EBRT is an effective treatment of metastatic bone pain.	II	[7], [9]
Single versus multi-fraction higher-dose EBRT	II	[1], [2], [3], [4], [5], [6], [8], [11], [12], [14], [15]

Evidence summary	Level	References
No dose response exists for pain response rates when comparing a single fraction of 8Gy versus multiple fractions ranging from 20Gy/5f to 30Gy/10f. That is, a single fraction of 8Gy is not worse than a course of multi-fraction treatment for the endpoint of pain response. Fracture rates following radiation are low (<5%). There is no consistent evidence that fracture rates or spinal cord compression rates are higher in single fractions. Single fractions are associated with a higher re-treatment rate.		

Evidence-based recommendation	Grade
Radiotherapy is an effective and well-tolerated treatment for metastatic bone pain. A single dose of 8Gy is as effective as higher fractionated doses (eg 20–30Gy) in reducing bone pain. The higher incidence of re-treatment with lower-dose single fraction regimens should be considered as part of the decision-making process.	**C**

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8.4.4.3 References

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8.4.5 Radiotherapy treatment of loco-regionally progressive disease

Contents

8.4.5.1 What is the evidence for the effect of radiotherapy in palliation of soft tissue disease of EBRT to the prostate for symptom treatment in locally advanced disease and to local metastases (such as the lymph nodes for symptom treatment such as lymphoedema and painful lymph nodes)?

The vast majority of patients with hormone-resistant prostatic carcinoma present with symptomatic bony metastases as their major symptom. There is a subset of patients, however, who present with significant pelvic symptoms (obstructive urinary symptoms, bleeding, rectal obstruction, pelvic and rectal pain) relating to locally progressive disease with or without symptomatic bony disease. The median survival of these men with small-

volume distant disease can be around 18–24 months and 6–12 months in those with more extensive disease. The optimal management of these patients remains far from clear. There are no randomised studies addressing the role of pelvic radiotherapy. However a number of retrospective studies suggest that a fractionated course of high-dose palliative pelvic radiation treatment can be extremely useful in obtaining growth restraint and alleviating the symptoms arising from the disease process.[1][2][3][4][5][6][7][8][9] Bleeding (haematuria) responds particularly well. Similar results were found in a more recent case series.[10]

A small subset of patients can also present with significant metastatic nodal disease within the pelvis, abdomen, chest and supraclavicular or lower neck region. The enlarged nodes can result in significant pain or obstructive symptoms due to the extrinsic compression on the adjacent organs. No randomised or retrospective studies have specifically addressed the role of radiation treatment in this setting. It is unlikely that any such studies will be undertaken.

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8.4.5.2 Evidence summary and recommendations

Evidence summary	Level	References
Although there are no randomised prospective trials to address whether radiotherapy has a beneficial effect on incurable prostate cancer and its soft tissue metastases, the question of benefit remains clinically important. Therefore, nine case series have been reviewed noting that these all pertain to locally advanced prostate cancer. There were no significant publications reviewing soft tissue metastases.	IV	[1], [2], [3], [4], [5], [6], [7], [8], [9]

Evidence-based recommendation	Grade
Radiotherapy can be considered for palliation of symptoms secondary to locally progressive disease.	**D**

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8.4.5.3 References

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10. ↑ Hindson B, Turner S, Do V. *Palliative radiation therapy for localized prostate symptoms in hormone refractory prostate cancer.* Australas Radiol 2007 Dec;51(6):584-8 Available from: http://www.ncbi.nlm.nih.gov/pubmed/17958697.

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8.4.5.4 Appendices

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8.4.6 Radiotherapy alone for spinal cord compression

Contents

8.4.6.1 What is the benefit of EBRT alone given for malignant spinal cord compression?

Spinal cord compression/nerve root compression (with or without surgery)

Spinal cord compression is an oncological emergency. It is a potentially devastating complication of metastatic prostate cancer that can result in pain, paraplegia, incontinence and loss of independence. It is not uncommon for sequelae of metastatic disease to occur in between 1% and 12% of patients.[1] No randomised controlled trials were found that examined treatments for spinal cord compression specifically for prostate cancer patients. Therefore, the systematic reviews were broadened to cover any trials that included prostate cancer patients.

Radiotherapy is an effective and well-tolerated treatment for metastatic bone pain. It has been the cornerstone of management for malignant spinal cord compression (MSCC) for decades as it is a noninvasive approach and associated with relatively low toxicity. Its effectiveness is based largely on retrospective outcomes from single institution series. There are no randomised trials comparing radiotherapy alone with either surgery alone or dexamethasone alone for malignant spinal cord compression. There is one randomised trial of 276 patients comparing two fractionation schedules (16Gy/2f vs 30Gy/8f) that gives outcome data of radiation alone.[2] In this trial only 14% of the entire cohort were prostate patients.

The Maranzano[2] trial confirms the importance of radiotherapy in the management of spinal cord compression, with 90% of ambulatory patients still walking at one month and 28% of non-ambulatory patients regaining ability to walk.[2] However, regaining ambulation if paraplegic is rare. More thanhalf of patients experienced pain relief but overall survival was poor, with median survival of four months. Although no significant differences in the fractionation schedules were seen, clinically significant differences could not be excluded. One-year survival was 18% for the longer fractionation versus 10% with the shorter approach. Five (versus none) infield recurrences were seen in the shorter fractionation group.

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8.4.6.2 Evidence summary and recommendations

Evidence summary	Level	References
There are no randomised trials comparing radiotherapy with either surgery or dexamethasone alone for spinal cord compression. There is one randomised trial comparing two different fractionation schedules for unfavourable risk malignant spinal cord compression. It demonstrated no significant differences between the schedules, though clinically important differences cannot be excluded	II	[2]

Evidence-based recommendation	Grade
For patients with malignant spinal cord compression the use of radiation is recommended.	**D**

Evidence-based recommendation	Grade
The optimal fractionation schedule of radiotherapy is unknown.	

Evidence-based recommendation	Grade
Patients being treated with radiation for spinal cord compression should be given dexamethasone at time of diagnosis.	**B**

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8.4.6.3 References

1. ↑ Tazi H, Manunta A, Rodriguez A, Patard JJ, Lobel B, Guillé F. *Spinal cord compression in metastatic prostate cancer.* Eur Urol 2003 Nov;44(5):527-32 Available from: http://www.ncbi.nlm.nih.gov/pubmed/14572749.
2. ↑ 2.0 2.1 2.2 2.3 Maranzano E, Bellavita R, Rossi R, De Angelis V, Frattegiani A, Bagnoli R, et al. *Short-course versus split-course radiotherapy in metastatic spinal cord compression: results of a phase III, randomized, multicenter trial.* J Clin Oncol 2005 May 20;23(15):3358-65 Available from: http://www.ncbi.nlm.nih.gov/pubmed/15738534.

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8.4.6.4 Appendices

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8.4.7 Surgery in malignant spinal cord compression

Contents

8.4.7.1 What is the role of surgery in the treatment of malignant spinal cord compression?

The role for surgery has long been controversial in malignant spinal cord compression from metastatic prostate cancer. It is acknowledged that the outcomes with radiotherapy alone are suboptimal, especially if patients are non-ambulatory or paraplegic at presentation. However, clinicians had concerns subjecting patients who are often unwell with a poor median survival to the rigors of surgery for a non-quantifiable degree of benefit. Also, it was not known whether surgery should consist of a decompression laminectomy alone (to relieve pressure on the spinal cord) or the more aggressive circumferential decompression laminectomy where the entire affected vertebrae is removed. Decompressive laminectomy should be considered when radiotherapy cannot be given due to previous treatment or progression during or shortly after radiotherapy.

There are only two randomised trials comparing surgery with radiotherapy versus radiotherapy alone.[1][2]The Patchell study of 101 patients (16% with prostate cancer) compared radiotherapy alone with direct circumferential decompression (with spinal stabilisation if spinal instability present) followed by radiotherapy.

The Patchell study demonstrated a clinically significant improvement with the addition of aggressive surgery to radiation only and was stopped early as it met pre-set termination criteria. For ambulatory patients at presentation, 94% versus 74% were walking post-treatment in the surgery and radiotherapy arms respectively. For non-ambulatory patients, the rates were 62% versus 19%. There was a median survival improvement of 126 versus 100 days (p=0.03) and a significant improvement in pain levels as judged by median mean daily morphine doses (p=0.002) with surgery.

Patients have to be carefully selected for the aggressive approach outlined in the Patchell study. They need to be fit for aggressive surgery, have a life expectancy of more than three months, have a single site of cord compression, have neurologic symptoms present, and have surgery within 48 hours if paraplegic. To be considered for this approach, hospitals would need adequate neurosurgical services and appropriate supportive care. This is likely to be available only in major teaching hospitals. The role of aggressive surgery for early malignant spinal cord compression seen on imaging but not causing neurologic symptoms is unclear.

The Young study of 29 patients (14% had prostate cancer) compared radiotherapy alone with laminectomy plus radiotherapy. This underpowered study demonstrated no benefit in ambulation or bladder function with the addition of a decompression laminectomy to radiotherapy. The Young study differed from the Patchell study in having significantly less aggressive surgery.

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8.4.7.2 Evidence summary and recommendations

Evidence summary	Level	References
There is one randomised trial demonstrating a significant clinical benefit with the addition of aggressive surgery (direct circumferential decompression) to radiotherapy for appropriate patients with symptomatic malignant spinal cord	II	[1]

Evidence summary	Level	References
compression		
The role of decompression laminectomy prior to radiotherapy is unknown, with one small trial demonstrating no benefit.	II	[2]

Evidence-based recommendation	Grade
For highly selected patients with malignant spinal cord compression, vertebrectomy with spinal stabilisation prior to radiotherapy should be considered. The role of decompression laminectomy prior to radiotherapy is unknown.	**C**

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8.4.7.3 References

1. ↑ [1.0] [1.1] Patchell RA, Tibbs PA, Regine WF, Payne R, Saris S, Kryscio RJ, et al. *Direct decompressive surgical resection in the treatment of spinal cord compression caused by metastatic cancer: a randomised trial.* Lancet ;366(9486):643-8 Available from: http://www.ncbi.nlm.nih.gov/pubmed/16112300.
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8.4.8 Steroids for malignant spinal cord compression

Contents

8.4.8.1 What is the efficacy of steroids for the treatment of malignant spinal cord compression?

Steroids such as dexamethasone are commonly utilised for patients with malignant spinal cord compression, often in conjunction with radiotherapy. They are thought to decrease oedema and thus prevent further impediment of blood supply. An anti-tumour effect in some cases may also play a role. Transient reductions in pain and improvement in neurologic function are well recognised with steroids alone. However, the absolute degree of benefit when combining steroids with radiotherapy is unknown and the recommended dosages are controversial.

There are three small low-quality randomised controlled trials evaluating the efficacy of steroids for malignant spinal cord compression. The Sorensen 1994 study[1] randomised 57 patients to receive high-dose dexamethasone (96mg initial bolus) combined with radiotherapy versus no dexamethasone and radiotherapy. Two trials compared the effects of different doses of dexamethasone as an adjuvant to radiotherapy[2][3] The Vecht 1989 trial randomised 37 patients to an initial dose of either 100mg or 10mg of dexamethasone in addition to radiotherapy.[3] The Graham 2006 trial[2] randomised 20 patients to an initial dose of either 96mg or 16mg dexamethasone combined with radiotherapy but was terminated prematurely because of poor accrual.[2] These studies included only a small (9%) or unspecified percentage of prostate patients and had wide variety of clinical presentations and imaging performed.

Even with small numbers, the Sorensen paper[1] demonstrated the importance of dexamethasone for malignant spinal cord compression, with 59% of those treated with dexamethasone (96mg initialbolus) in addition to radiotherapy ambulant at six months compared with 33% of those treated with radiotherapy alone (p=0.05). The addition of dexamethasone significantly (p=0.046) improved the probability of surviving with gait function in the year following treatment without a significant increase in serious toxicities. The Vecht trial comparing high and low doses of dexamethasone showed no difference in pain, ambulation rates or bladder function between the two arms but the low power of the study (37 patients) cannot exclude clinically important differences.

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8.4.8.2 Evidence summary and recommendations

Evidence summary	Level	References
There is one small trial of high-dose dexamethasone and radiotherapy versus radiotherapy alone. This demonstrated a significant improvement in ambulation rates in the steroid arm.	II	[1]
The optimal dose of steroids is unknown, with one small trial demonstrating no	II	

Evidence summary	Level	References
significant difference in efficacy of higher-dose dexamethasone over lower doses.		[3]

Evidence-based recommendation	Grade
Patients being treated with radiotherapy for malignant spinal cord compression should also receive dexamethasone.	**C**

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8.4.8.3 References

1. ↑ [1.0] [1.1] [1.2] Sorensen D, McCarthy M, Baumgartner B, Demars S. *Perioperative immunonutrition in head and neck cancer.* Laryngoscope 2009 Jul;119(7):1358-64 Available from: http://www.ncbi.nlm.nih.gov/pubmed/19459146.
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8.4.8.4 Appendices

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8.4.9 Hemibody external beam radiotherapy

Contents

8.4.9.1 What is the efficacy of Hemibody (widefield) external beam radiotherapy in the palliation of uncomplicated bone pain?

Hemibody radiotherapy refers to the practice of irradiation of either the lower body half (pelvis and legs) or the upper body half (upper lumbar spine, chest, arms with or without the skull). It was a commonly used treatment for prostate cancer with multifocal pain when effective chemotherapy or radionucleide therapy was not available.

There are no controlled trials comparing pain responses with and without hemibody radiotherapy.

One low-quality RCT (Poulter 1992, n=499, 33% prostate cancer patients[1]) examined whether hemibody radiation in addition to local radiation retarded disease progression for patients with moderately to severely painful single or multiple bone metastases. The addition of hemibody radiation (8Gy, single fraction) to local radiotherapy significantly retarded disease progression as evidenced by increase in lesion size (p=0.03) and number (p=0.01). However, in this study[1], hemibody radiation was associated with a significant increase in grades 3 and 4 haematological toxicity (p=0.004), with leukopenia being significantly worse (p=0.01).

A quasi-randomised controlled trial by Scarantino (n=144, 70% prostate cancer)[2] examined the effects of increasing the dose of hemibody irradiation in conjunction with local radiotherapy on progression and toxicity. This study was unable to show that increasing multi-fraction hemibody radiation dose from 10Gy to 20Gy significantly reduced the development of new metastases when given in conjunction with local radiotherapy.

A second low-quality RCT by Salazar 2001 (n=156, 32% prostate cancer)[3] examined escalating doses of hemibody radiotherapy without local radiotherapy. When given alone, increasing hemibody radiation dose as multi-fraction regimens from 8Gy to 15Gy[3] did not significantly improve overall pain responses (response rates 89% and 92%). However, it did significantly (p=0.016) improve complete pain responses without an apparent increase in grade 3–4 toxicity (16% at 8Gy and 8% at 15Gy).

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8.4.9.2 Evidence summary and recommendations

Evidence summary	Level	References
There are no controlled trials comparing pain responses with and without hemibody radiotherapy.	II	[1], [3]
Increasing hemibody radiation doses above 8Gy does not improve overall pain palliation.	III-1	[2]

Evidence summary	Level	References
There is no good evidence to support the use of fractionated hemibody irradiation over a single fraction. Adding hemibody radiation to local external beam radiotherapy while retarding progression increases grade 3–4 haematological toxicity.		

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8.4.9.3 References

1. ↑ [1.0] [1.1] [1.2] Poulter CA, Cosmatos D, Rubin P, Urtasun R, Cooper JS, Kuske RR, et al. *A report of RTOG 8206: a phase III study of whether the addition of single dose hemibody irradiation to standard fractionated local field irradiation is more effective than local field irradiation alone in the treatment of symptomatic osseous metastases.* Int J Radiat Oncol Biol Phys 1992;23(1):207-14 Available from: http://www.ncbi.nlm.nih.gov/pubmed/1374061.
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8.4.10 Unsealed radioisotopes

Contents

8.4.10.1 What is the effectiveness of unsealed radioisotopes in the management of bone pain from prostate cancer?

The administration of certain radioactive chemicals (radioisotopes) through the blood stream (as a single dose of an intravenous injection) offers one method of dealing with patients presenting with such multifocal pain. Such an approach has the advantage of not only relieving pain but also having some anti-tumour effect. The two isotopes that have been used in Australia include strontium 89 and samarium 153. The former has been more easily accessible and therefore used more commonly. These isotopes are characterised by low radiation emissions localised to the bone and have affinity for bone, especially honing onto areas where the affected bone responds to the presence of tumour cells by producing reactive bony tissue. (These areas can appear as abnormal dense areas referred to as osteoblastic metastases on X-rays.)

Nine RCTs have examined the effects of strontium 89 for the treatment of bone metastases. Two compared strontium 89 with placebo.[1][2] Four compared strontium 89 with active treatment arms such as local or hemi-body irradiation[3][4] or chemotherapy.[5][6] Two examined the addition of strontium 89 to local external beam radiotherapy[7][8] and two examined the addition of strontium 89 to chemotherapy.[5][9] The heterogeneity of study design renders low volumes of evidence about any specific treatment. In addition, only non-taxane chemotherapy was used in the chemotherapy trials. Therefore these trials lose their relevance in modern-day practice where taxanes are the first-line chemotherapeutic option of choice. As a result they were not considered further in this analysis. Four RCTs examined the effects of samarium 153 for the treatment of bone metastases. Two randomised trials compared samarium with placebo[10][11] and three studies compared different doses of Samarium.[10][12][13] There are no randomised trials comparing samarium with other radioisotopes, chemotherapy or external beam irradiation.

Regrettably, the majority of the remaining studies have flaws in that they have used small sample sizes, are not head-to-head comparisons, utilise different criteria to measure response to pain, and some studies are not limited to patients with metastatic prostate cancer alone.[1][14][12][13] Furthermore, while the patients in these studies appear similar to prostate cancer patients seen in palliative care practice, these studies were conducted in the pre-taxane chemotherapy and bisphosphonate era. As a result, the findings may not be generalisable to current Australian medical practice where many of the men with bone metastases might have been pre-treated with chemotherapy (taxane-based) or bisphosphonates. The potential for increased bone marrow suppression in this setting must to be taken into consideration before administering the radioisotope.

Pain control

There were four studies examining strontium 89 for metastatic bone pain relief.[1][2][3][7][8] These varied in follow up, doses, regimen and endpoint reporting. The largest study with the highest dose showed a statistically significant decrease in analgesic use when strontium was added to local radiotherapy.[7][8] The RCT comparing strontium 89 with external beam radiotherapy suggested that these treatments were equivalent.[3] The results of the two small placebo RCTs[1][2] were conflicting.

The two studies comparing samarium 153 with placebo show a trend towards pain relief with samarium 153. The prostate-cancer-specific study[11] with the largest number of participants (n=152), showed a statistically significant benefit. All three studies examining dose show a trend towards better pain relief with higher dose. However, the size of the effect could not be adequately assessed in twoof these studies[10][12]and in the third study[13] with small numbers of prostate cancer patients (n=12), the effects were not significant.

Samarium 153 has a shorter half-life and thus it has been hypothesised may have a quicker response. However, there is currently no evidence available to support this.

Five RCTs examined the effect of strontium 89 on disease progression in men with prostate cancer.

Both trials examining the addition of strontium 89 to external beam radiotherapy suggested that strontium 89 delays progression of bony disease. In the larger (n=126) and better-quality study the delay is statistically significant,[7][8] whereas in the second study[14] the delay is not statistically significant for the prostate cancer patient subgroup. In one of the trials comparing strontium 89 with external beam radiotherapy, strontium-89 resulted in a statistically significant delay in disease progression,[3] whereas in the other, local external beam radiotherapy was associated with better progression-free survival.[4]

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8.4.10.2 Evidence summary and recommendations

Evidence summary	Level	References
Men with hormone refractory prostate cancer and painful bone metastases **strontium 89** Limited evidence suggests that strontium 89 is effective as a treatment for pain relief. There is no randomised control trial evidence comparing the efficacy of strontium 89 with that of modern-day taxane-based chemotherapy or bisphosphonates	II	[1], [2], [3], [7], [8]
samarium 153 A small volume of low- to moderate-quality grade II consistent evidence suggests that samarium 153 is an effective treatment for relief of bone metastases pain. There is only one randomised trial showing a benefit. There is no randomised control trial evidence comparing its efficacy with that of strontium 89, modern-day taxane-based chemotherapy or bisphosphonates.	II	[10], [11], [12], [13]

Evidence-based recommendation	Grade
Unsealed radioisotopes may be considered for the management of multifocal bone pain alongside other options of treatment in patients with hormone refractory prostate cancer.	C

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8.4.10.3 References

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5. ↑ 5.0 5.1 Sherman EJ, Pfister DG, Ruchlin HS, Rubin DM, Radzyner MH, Kelleher GH, et al. *The Collection of Indirect and Nonmedical Direct Costs (COIN) form: a new tool for collecting the invisible costs of androgen independent prostate carcinoma.* Cancer 2001 Feb 15;91(4):841-53 Available from: http://www.ncbi.nlm. nih.gov/pubmed/11241254.
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8. ↑ 8.0 8.1 8.2 8.3 8.4 Porter AT, McEwan AJ, Powe JE, Reid R, McGowan DG, Lukka H, et al. *Results of a randomized phase-III trial to evaluate the efficacy of strontium-89 adjuvant to local field external beam irradiation in the management of endocrine resistant metastatic prostate cancer.* Int J Radiat Oncol Biol Phys 1993 Apr 2;25(5):805-13 Available from: http://www.ncbi.nlm.nih.gov/pubmed/8478230.

9. ↑ Nilsson S, Strang P, Ginman C, Zimmermann R, Edgren M, Nordström B, et al. *Palliation of bone pain in prostate cancer using chemotherapy and strontium-89. A randomized phase II study.* J Pain Symptom Manage 2005 Apr;29(4):352-7 Available from: http://www.ncbi.nlm.nih.gov/pubmed/15857738.
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8.4.11 Unsealed radioisotopes and overall survival

Contents

8.4.11.1 Do unsealed radioisotopes improve survival in metastatic prostate cancer?

Six RCTs report survival outcomes. Results were conflicting for the four strontium 89 trials. The trial comparing strontium 89 alone with placebo reported a statistically significant improvement in survival in patients receiving strontium 89.[1] This was one old trial with small sample size (n=44) and only actuarial survival was reported. In contrast, the addition of strontium to local radiotherapy appeared to provide no survival benefit.[2][3] The larger (n=203) trial comparing strontium 89 with local external beam radiotherapy reported a statistically significant improvement in survival in patients receiving radiotherapy[4], whereas the smaller trial comparing strontium 89 with local (n=111) or hemibody (n=106) external beam radiotherapy showed a beneficial but not statistically significant improvement in survival with strontium 89.[5] No survival benefit was seen with samarium 153.[6][7]

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8.4.11.2 Evidence summary and recommendations

Evidence summary	Level	References
Men with hormone refractory prostate cancer and painful bone metastases The trials examining the effect of unsealed radioisotopes on overall survival have been heterogeneous in study design, contained small patient numbers and provided conflicting results. As such no firm conclusions can be made. The role of radioisotopes in the context of modern-day systemic therapy (chemotherapy and bisphosphonates) has not been defined.	II	[1], [5], [8], [3], [4], [6], [7]

Evidence-based recommendation	Grade
The impact of unsealed radioisotopes on overall survival in men with castrate-resistant metastatic prostate cancer is undefined. The relative roles of unsealed radioisotopes and the newer chemotherapeutic agents (e.g. taxanes) and bisphosphonates have also not been defined.	**D**

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8.4.11.3 References

1. ↑ [1.0] [1.1] Buchali K, Correns HJ, Schuerer M, Schnorr D, Lips H, Sydow K. *Results of a double blind study of 89-strontium therapy of skeletal metastases of prostatic carcinoma.* Eur J Nucl Med 1988;14(7-8):349-51 Available from: http://www.ncbi.nlm.nih.gov/pubmed/2460352.

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8.4.12 Unsealed radioisotopes and quality of life

Contents

8.4.12.1 What is the evidence that quality of life is improved with unsealed radioisotopes in prostate cancer?

There are four low- to medium-quality RCTs testing the effect of treatment with Strontium-89 that assess a 'quality of life endpoint'. The assessed quality of life endpoints were different, in no trial was a validated instrument used, and in only one trial was assessment solely patient reported. Neither study comparing strontium 89 with external beam radiation showed statistical evidence of effect.[1][2] In the study comparing strontium 89 with placebo[3]and the study examining the effect of addition of strontium 89 to local external beam radiation,[4][5] the strontium treatment appeared to have modest but inconsistent beneficial effects on quality of life endpoints.

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8.4.12.2 Evidence summary and recommendations

Evidence summary	Level	References
Men with hormone refractory prostate cancer and painful bone metastases There are few studies examining the effect of strontium 89 on quality-of-life endpoints and these are generally dissimilar in design and the examined endpoint. The design of these studies is not high quality. In studies that show some beneficial effect, the effects are modest at best, with many patients also exhibiting a worsening of quality-of-life endpoints.	II	[3], [1], [2], [4], [5]

Evidence-based recommendation	Grade
It is not known what effect unsealed radioisotopes have on quality of life for men with metastatic prostate cancer.	**C**

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8.4.12.3 References

1. ↑ 1.0 1.1 Quilty PM, Kirk D, Bolger JJ, Dearnaley DP, Lewington VJ, Mason MD, et al. *A comparison of the palliative effects of strontium-89 and external beam radiotherapy in metastatic prostate cancer.* Radiother Oncol 1994 Apr;31(1):33-40 Available from: http://www.ncbi.nlm.nih.gov/pubmed/7518932.

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8.4.13 Toxicity of unsealed radioisotopes

Contents

8.4.13.1 What is the toxicity of unsealed radioisotopes for treatment of metastatic prostate cancer?

As these radioisotopes are taken up by bone, they have the potential to suppress the bone marrow and result in low red and white blood cell and platelet counts which can then lead to dependence on blood transfusions, increased risk of infections and easy bruising. Patients who have low blood counts at the outset would generally be regarded as being unsuitable and ineligible for this treatment.

All the strontium 89 and samarium 153 trials reported toxicity outcomes.

Thrombocytopenia and/or leucopenia were observed to some extent in all studies. strontium 89 tends to show a similar or worse effect on thrombocytopenia and leucopenia than hemibody and local irradiation[1][2], more effect than 'best supportive care' [3][4], and statistically significantly more effect when added to localised radiation.[5][6] There is no good evidence that strontium 89 causes significant adverse effects other than haematological. All the samarium trials demonstrate a reduction in platelets and white cell count with samarium 153. In one trial this effect is statistically significant for white blood cell toxicity.[7] However, the development of grade III or IV neutropaenia is uncommon (<15%). There are no data on increased risk for fractures.

An association of radioisotope therapy with life-threatening haematological toxicity would be of high clinical impact, particularly when other treatment options for palliation are available. The small numbers in these studies mean that they are unlikely to be sufficiently powered to exclude a meaningful increase in fatal adverse events associated with the use of radioisotopes.

Furthermore, currently patients in Australia considered for radioisotope treatment are likely to bemore heavily pre-treated with chemotherapy than those entered into these studies. The haematological toxicity is possibly much more marked in these pre-treated patients, thus great care must be made extrapolating these results to prostate cancer patients who have been pre-treated with chemotherapy or who have significant marrow infiltration prior to starting radiotherapy.

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8.4.13.2 Evidence summary and recommendations

Evidence summary	Level	References
Men with hormone refractory prostate cancer and painful bone metastases **strontium 89** At the doses administered, and in a population of patients who were not pre-treated with chemotherapy, strontium 89 appears associated with mild haematological toxicity. The possibility of significant serious adverse events cannot be excluded by the published trials, compared with the use of best supportive care or localised radiation.	II	[3], [4], [1], [2], [5], [6], [8]

Evidence summary	Level	References
samarium 153 The limited evidence demonstrates that samarium 153 results in falls in white cell counts and platelets. However, in patients with adequate marrow reserve, the development of grade III or IV neutropaenia or thrombocytopaenia is uncommon (<15%) and clinically significant toxicity is rare. There is no randomised evidence comparing samarium with other radioisotopes such as strontium.	II	[7], [9], [10], [11]

Evidence-based recommendation	Grade
Unsealed radioisotopes alone may be associated with higher haematological adverse events compared with supportive care or localised radiation, although overall these rates are low. Unsealed radioisotopes in combination with other treatments such as radiotherapy have higher rates of serious toxicity than radiotherapy alone. The toxicity of unsealed radioisotopes in combination with modern chemotherapy (taxanes) has not yet been defined and caution should be exercised if such combinations are considered.	**C**

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8.4.13.3 References

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8.4.14 Chemotherapy - Efficacy and toxicity

Contents

8.4.14.1 Does cytotoxic chemotherapy give a survival benefit or any other benefits in terms of quality of life improvement, control of pain or other symptoms compared to patients not receiving chemotherapy or receiving different types of chemotherapy?

Metastatic prostate cancer refers to patients in whom the cancer has spread beyond the primary site. This chapter deals with adenocarcinoma only. Most commonly, metastatic disease involves bone and lymph nodes and less commonly, viscera such as the lungs and liver. Patients with metastatic prostate cancer may be considered as hormone naïve or castration-resistant.

8.4.14.1.1 Hormone-naïve metastatic prostate cancer

Hormone-naïve patients are treated with hormone deprivation therapies including gonadotrophin releasing hormone (GnRH) agonists, orchidectomy and anti-androgens. The response rate is high and the median duration of response is approximately 18–24 months,[1] with 20% of patients living five years or more.

Small, non-informative RCTs performed over the past 20 years using minimally active chemotherapy demonstrated no benefit from the use of cytotoxic agents in the hormone-naïve setting.[2] Continuing large phase III studies are currently examining the role of chemotherapy, which is active in the castrate-resistant setting, in combination with androgen deprivation therapy in the hormone-naïve setting.

8.4.14.1.2 Castration-resistant prostate cancer

Castration-resistant prostate cancer (CRPC) includes patients with evidence of disease progression despite castrate levels of testosterone. About 20% of these patients may initially respond to secondline hormone manipulations, but almost all ultimately progress. At least three clinical states exist:

- patients with a rising PSA who are asymptomatic and have no objective radiologic evidence of metastatic disease
- patients with a rising PSA who are asymptomatic but who do have objective radiologic evidence

of metastatic disease

- patients with a rising PSA who have objective radiologic evidence of metastatic disease and

symptoms.

In general, the first group of patients (asymptomatic rising PSA) are not treated with chemotherapy but may be suitable candidates for clinical trials and/or second-line hormone manipulations. The second and third groups are candidates for the use of systemic chemotherapy as discussed below or as part of a trial.

Old studies examined a variety of chemotherapy agents in combination or as monotherapy. These studies were generally of poor quality, had limited patient numbers, used agents with low efficacy and were constrained by difficulties in evaluating efficacy in this patient population.

Modern chemotherapy for CRPC was established by the studies of Tannock et al and Kantoff et al.[3][4] Both studies examined the efficacy of mitoxantrone against a control arm of prednisolone orhydrocortisone respectively. Tannock et al documented that treatment with mitoxantrone resulted in a significant improvement in pain, quality of life and PSA response. There was no survival benefit although this was not a study endpoint. Kantoff et al reported similar outcomes.

Subsequently, two pivotal large multicentre phase III studies[5][6] have demonstrated a survival benefit while maintaining improvements in quality of life for patients receiving docetaxel-based chemotherapy for their CRPC. These two studies form the basis for the current standard of care in Australia, docetaxel chemotherapy for CRPC.

Tannock et al (TAX 327 study) enrolled 1006 patients who were randomly assigned to docetaxel 30mg/m2 weekly for five of every six weeks, docetaxel 75mg/m2 every three weeks or mitoxantrone 12mg/m2 every three weeks.[5] All patients received 5mg bd of prednisolone. GnRH was continued. The majority of patients were Karnofsky performance score >70 and nearly half were asymptomatic. Up to ten cycles were planned for mitoxantrone and the three-weekly docetaxel group where median cycles completed were 5 and 9.5 respectively. Median survival was superior in the three-weekly docetaxel arm compared with mitoxantrone arm (18.9 months and 16.5 months; p=0.009). Three weekly docetaxel also led to better pain control (35% versus 22%; p = 0.01), improvement in quality of life (22% improvement versus 13 % improvement; p=0.005) and PSA decline of >50% (48% vs 32% P <0.001). In contrast, weekly docetaxel when compared with mitoxantrone did not result in statistically significant improvements in survival or pain control.

Petrylak et al (SWOG) reported superior survival for a combination of docetaxel and estramustine compared with mitoxantrone among 770 men (17.5 months versus 15.6 months; p=0 .02).[6] All patients received 5mg bd of prednisone. Pain relief was similar between arms.

The major side effects of docetaxel were consistent with the known side-effects profile including: alopecia (65%), lethargy (53%), nail changes (30%), neutropenia (32%) diarrhoea (32%) and neuropathy (30%). The incidence of neutropenic sepsis was 3–5% and the incidence of treatmentrelated death was less than 1%.

The combination of docetaxel and estramustine is not relevant to Australia as estramustine is not available. Further, the relatively high risk of thrombo-embolism and other toxicities has resulted in estramustine being dropped from the combination.

A number of issues remain as to the optimal use of docetaxel in patients with CRPC:

- how to manage men of poor performance status and/or those with organ dysfunction
- the benefit and timing of docetaxel chemotherapy in asymptomatic men remains unresolved
- the most efficacious sequencing of docetaxel and radioisotope therapy has not been addressed

- numerous studies are examining the effect of adding agents to docetaxel in men with CRPC
- the most effective form of second-line (post-docetaxel) systemic therapy requires exploration.
- see <http://clinicaltrials.gov> for currently registered trials.

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8.4.14.2 Evidence summary and recommendations

Evidence summary	Level	References
Mitoxantrone and steroids offers better pain relief and quality of life than steroids alone.	II	[3], [4]
Docetaxel and prednisone is associated with better survival, pain relief and quality of life than mitoxantrone and prednisone.	II	[5]
Compared with mitoxantrone and prednisone, docetaxel and estramustine improves survival without any effect on quality of life or pain.	II	[6]
In comparison to mitoxantrone, docetaxel causes more grade 3 or 4 neutropenia, fatigue, alopecia, nail changes, diarrhoea, stomatitis, tearing, sensory neuropathy, dyspnoea, changes in taste and peripheral oedema. Mitoxantrone causes more impairment in left ventricular function than docetaxel. Docetaxel and estramustine in combination cause more cardiovascular events, neutropenic fevers, neurologic and metabolic disturbances and nausea and vomiting than mitoxantrone and prednisone.	II	[5], [7]

Evidence-based recommendation	Grade
Docetaxel in combination with prednisone is appropriate in the first line setting to improve survival, pain and quality of life in good performance patients with castrate-resistant metastatic prostate cancer.	**B**

Evidence-based recommendation	Grade
The combination of mitoxantrone and prednisolone also offers palliative benefit but no survival benefit compared to docetaxel.	**C**

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8.4.14.3 References

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8.4.15 Chemotherapy vs radiotherapy or radioisotopes

8.4.15.1 Has the effectiveness of chemotherapy been compared to external beam radiotherapy or radio-isotopes (strontium or samarium) in a randomised study?

Systematic search was performed.

Recommendation cannot be made as insufficient relevant evidence.

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8.4.16 Radioisotopes and chemotherapy

8.4.16.1 Can radio-isotopes (strontium or samarium) be used at the same time as (simultaneously with) chemotherapy (combined therapy) without excessive toxicity?

Systematic search was performed.

Recommendation cannot be made as insufficient relevant evidence.

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9 Palliative care

Contents

9.1 Palliative care

Palliative care has been defined in a number of ways. The World Health Organization (WHO) has defined palliative care as

...an approach that improves the quality of life of patients and their families facing the problem associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual.'

Palliative care:

- provides relief from pain and other distressing symptoms;
- affirms life and regards dying as a normal process;
- intends neither to hasten nor postpone death;
- integrates the psychological and spiritual aspects of patient care;
- offers a support system to help patients live as actively as possible until death;
- offers a support system to help the family cope during the patients illness and in their own bereavement;
- uses a team approach to address the needs of patients and their families, including bereavement counselling, if indicated; will enhance quality of life, and may also positively influence the course of illness;
- is applicable early in the course of illness, in conjunction with other therapies that are intended to prolong life, such as chemotherapy or radiation therapy, and includes those investigations needed to better understand and manage distressing clinical complications.[1]

This last point highlights that palliative care should be an active approach to patient management and, when appropriate, integrated into continuing approaches to disease control.

The WHO has also advocated the integration of comprehensive palliative care and pain management into cancer control programs. Palliative care programs are charged with providing pain relief, control of other symptoms, and psychosocial and spiritual support.[2]This approach has been supported by the Australian Government through its National Palliative Care Strategy,[3] and Palliative Care Australia, the national peak body for palliative care, which sets a goal that ‘all people who have a life limiting illness are able to access timely, high quality care appropriate to their needs’.[4]

These plans highlight the importance of all health professionals, from primary care through all specialties, recognising their role in the provision of palliative care, with specialist palliative care services focussing on those patients with more complex needs. The need for access to palliative care is also recognised in other prostate cancer guidelines, again emphasising that it should be available when needed and not limited to the end of life.[5]

Palliative care delivery has been characterised by a team working together to provide integrated care in all domains—physical, emotional, psychological and spiritual. The team can involve a range of medical, nursing and allied health personnel, including psychologists, social workers,physiotherapists, occupational therapists, speech pathologists and dietitians as well as pastoral care workers and volunteers. Many of the studies refer to this type of care as 'multidisciplinary' care but it is now more usually described as 'interdisciplinary' care to distinguish it from the multidisciplinary cancer care team which is assembled to plan cancer management.

Although there has been little written in relation to the specific palliative care needs of men with metastatic prostate cancer, there is ample evidence of high symptom prevalence in patients with advanced cancer. Teunissen et al reported a systematic review of 44 studies of symptom prevalence in patients with advanced cancer, with a total of 25,074 patients.[6] Fatigue (74%) was the most prevalent symptom, followed by pain (71%), lack of energy (69%), weakness (60%) and anorexia (53%). This clinical pattern is relevant to men with advanced metastatic prostate cancer.

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9.1.1 Models of Palliative care

Interdisciplinary palliative care is widely available in the Australian healthcare context. The precise model of practice may vary depending on the location of care, the delineation of roles and the focus of the palliative care needs. Specialist palliative care services may be predominantly community based or consist of hospital-based consultative teams. These specialist services might also be delivered in inpatient palliative care units or in a hospice where the team is responsible for its own patient care and beds. The location of the team and its role may influence the timing of referral. Specialist palliative care services working in close association with oncology units can provide easy access to pain and symptom management for oncology patients.

The provision of palliative care is now seen to be an integral part of the standard clinical practice of any healthcare professional. In the case of men with metastatic prostate cancer these health professionals will include urologists and radiation and medical oncologists. In the community, care will be coordinated by general practitioners with support from community nursing services and other support services. All clinicians should feel comfortable in initiating palliative care or in making appropriate referrals when more advice or support is needed from a specialist palliative care practitioner.

In rural and remote Australia, access to some elements of the model may be limited. In these settings and in many community settings, care would usually be coordinated by primary care practitioners, in particular general practitioners and nurses. Limited resources and personnel in rural and remote settings mean that elements of direct interdisciplinary support seen in larger centres, such as multidisciplinary education and counselling interventions,[7] may not be readily available in all settings and that this support and advice is usually provided periodically or through telephone contact to these practitioners by interdisciplinary specialist palliative care teams.

In addition, nursing homes in Australia are the site of much end-of-life care for older people, and delivery of palliative care to this population is also relevant.

In men with metastatic prostate cancer, there is considerable need for coordinated interdisciplinary palliative care from generalist or specialist services. Responding to this need could have a major clinical impact given the size of the population affected by metastatic prostate cancer, but would require an increase in resources for specialist palliative care services as well as continuing education for other health professionals.

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9.2 Literature search on three key questions

9.2.1 Clinical questions

- In men with metastatic prostate cancer, what is the evidence that referral to specialist palliative care car assist in supporting patient's decision-making and treatment planning processes?
- In men with metastatic prostate cancer, what is the evidence that referral to specialist palliative care car assist in symptom control?
- In men with metastatic prostate cancer, what is the evidence that referral to specialist palliative care car assist patients and their families in providingeffective end-of-life care?

Clinical questions considered, but for which no evidence was found

- In men with advanced prostate cancer what palliative interventions (including use of analgesics and co-analgesics) can assist in pain control?
- In men with advanced prostate cancer, what interventions may ameliorate or minimise the symptoms of fatigue?

The search on effective end-of-life care included a review of site of care and site of death, family caregiver satisfaction with care, and impact on the burden of providing end of life care. Although there were no randomised controlled trials specific to metastatic prostate cancer, there were a number of randomised controlled studies identified that dealt with palliative care interventions for patients with advanced cancer, including men with prostate cancer. It was therefore felt that those studies that reached at least Level II evidence with a size of effect rating of at least 2, could be generalised to men with metastatic prostate cancer. The studies covered a wide spectrum of different interventions ranging from educational and counselling sessions, to nurse-led interventions for care at home, and full interdisciplinary palliative care team involvement in care. Double-blinding was not possible, and loss to follow-up through death or deterioration was high. Individual studies were generally small and underpowered, and pooling of data to gain power was not possible because of the problem of heterogeneity of interventions. Concealment of randomisation was also problematic with only three studies overall rated 'high' for quality of concealment of treatment allocation schedule.[8][9][10]

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9.3 Summary

Men with metastatic prostate cancer should be referred for interdisciplinary palliative care to assist in symptom control and provide emotional, social and spiritual support. This support has been shown to relieve caregiver burden and assist families and carers in providing effective end-of-life care. The involvement of an interdisciplinary palliative care team can improve symptom control and assist in the emotional, spiritual and social wellbeing in patients with advanced cancer.

At any time in the course of the illness, a patient and his family may need support from a communitybased service or a hospital-based consultative team, or even assessment and management by an inpatient palliative care unit. Often palliative care services that work closely with oncology units will gain earlier referrals for pain and symptom management for their prostate cancer patients. The nature of prostate cancer and the age of onset often mean that other medical conditions and co-morbidities may well require the involvement of aged care and geriatric support services at this time as well.

These factors highlight the importance of continuing research to support palliative care in the management of prostate cancer. All health professionals involved in the care of men with metastatic prostate cancer should feel comfortable in initiating palliative care or in making an appropriate referral for specialist interdisciplinary palliative care.

As to how best discuss prognosis and end-of-life issues with the patient and his care-givers, please see *Clinical practice guidelines for communicating prognosis and end-of-life issues with adults in the advanced stages of a life-limiting illness, and their caregivers.*[11]

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9.1 Introduction

Contents

9.1.1 Palliative care

Palliative care has been defined in a number of ways. The World Health Organization (WHO) has defined palliative care as

...an approach that improves the quality of life of patients and their families facing the problem associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual.'

Palliative care:

- provides relief from pain and other distressing symptoms;
- affirms life and regards dying as a normal process;
- intends neither to hasten nor postpone death;
- integrates the psychological and spiritual aspects of patient care;
- offers a support system to help patients live as actively as possible until death;
- offers a support system to help the family cope during the patients illness and in their own bereavement;
- uses a team approach to address the needs of patients and their families, including bereavement counselling, if indicated; will enhance quality of life, and may also positively influence the course of illness;
- is applicable early in the course of illness, in conjunction with other therapies that are intended to prolong life, such as chemotherapy or radiation therapy, and includes those investigations needed to better understand and manage distressing clinical complications.[1]

This last point highlights that palliative care should be an active approach to patient management and, when appropriate, integrated into continuing approaches to disease control.

The WHO has also advocated the integration of comprehensive palliative care and pain management into cancer control programs. Palliative care programs are charged with providing pain relief, control of other symptoms, and psychosocial and spiritual support.[2]This approach has been supported by the Australian Government through its National Palliative Care Strategy,[3] and Palliative Care Australia, the national peak body for palliative care, which sets a goal that 'all people who have a life limiting illness are able to access timely, high quality care appropriate to their needs'.[4]

These plans highlight the importance of all health professionals, from primary care through all specialties, recognising their role in the provision of palliative care, with specialist palliative care services focussing on those patients with more complex needs. The need for access to palliative care is also recognised in other prostate cancer guidelines, again emphasising that it should be available when needed and not limited to the end of life.[5]

Palliative care delivery has been characterised by a team working together to provide integrated care in all domains—physical, emotional, psychological and spiritual. The team can involve a range of medical, nursing and allied health personnel, including psychologists, social workers,physiotherapists, occupational therapists, speech pathologists and dietitians as well as pastoral care workers and volunteers. Many of the studies refer to this type of care as 'multidisciplinary' care but it is now more usually described as 'interdisciplinary' care to distinguish it from the multidisciplinary cancer care team which is assembled to plan cancer management.

Although there has been little written in relation to the specific palliative care needs of men with metastatic prostate cancer, there is ample evidence of high symptom prevalence in patients with advanced cancer. Teunissen et al reported a systematic review of 44 studies of symptom prevalence in patients with advanced cancer, with a total of 25,074 patients.[6] Fatigue (74%) was the most prevalent symptom, followed by pain (71%), lack of energy (69%), weakness (60%) and anorexia (53%). This clinical pattern is relevant to men with advanced metastatic prostate cancer.

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9.1.1.1 Models of Palliative care

Interdisciplinary palliative care is widely available in the Australian healthcare context. The precise model of practice may vary depending on the location of care, the delineation of roles and the focus of the palliative care needs. Specialist palliative care services may be predominantly community based or consist of hospital-based consultative teams. These specialist services might also be delivered in inpatient palliative care units or in a hospice where the team is responsible for its own patient care and beds. The location of the team and its role may influence the timing of referral. Specialist palliative care services working in close association with oncology units can provide easy access to pain and symptom management for oncology patients.

The provision of palliative care is now seen to be an integral part of the standard clinical practice of any healthcare professional. In the case of men with metastatic prostate cancer these health professionals will include urologists and radiation and medical oncologists. In the community, care will be coordinated by general practitioners with support from community nursing services and other support services. All clinicians should feel comfortable in initiating palliative care or in making appropriate referrals when more advice or support is needed from a specialist palliative care practitioner.

In rural and remote Australia, access to some elements of the model may be limited. In these settings and in many community settings, care would usually be coordinated by primary care practitioners, in particular general practitioners and nurses. Limited resources and personnel in rural and remote settings mean that elements of direct interdisciplinary support seen in larger centres, such as multidisciplinary education and counselling interventions,[7] may not be readily available in all settings and that this support and advice is usually provided periodically or through telephone contact to these practitioners by interdisciplinary specialist palliative care teams.

In addition, nursing homes in Australia are the site of much end-of-life care for older people, and delivery of palliative care to this population is also relevant.

In men with metastatic prostate cancer, there is considerable need for coordinated interdisciplinary palliative care from generalist or specialist services. Responding to this need could have a major clinical impact given the size of the population affected by metastatic prostate cancer, but would require an increase in resources for specialist palliative care services as well as continuing education for other health professionals.

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9.1.2 Literature search on three key questions

9.1.2.1 Clinical questions

- In men with metastatic prostate cancer, what is the evidence that referral to specialist palliative care car assist in supporting patient's decision-making and treatment planning processes?
- In men with metastatic prostate cancer, what is the evidence that referral to specialist palliative care car assist in symptom control?
- In men with metastatic prostate cancer, what is the evidence that referral to specialist palliative care car assist patients and their families in providingeffective end-of-life care?

Clinical questions considered, but for which no evidence was found

- In men with advanced prostate cancer what palliative interventions (including use of analgesics and co-analgesics) can assist in pain control?
- In men with advanced prostate cancer, what interventions may ameliorate or minimise the symptoms of fatigue?

The search on effective end-of-life care included a review of site of care and site of death, family caregiver satisfaction with care, and impact on the burden of providing end of life care. Although there were no randomised controlled trials specific to metastatic prostate cancer, there were a number of randomised controlled studies identified that dealt with palliative care interventions for patients with advanced cancer, including men with prostate cancer. It was therefore felt that those studies that reached at least Level II evidence with a size of effect rating of at least 2, could be generalised to men with metastatic prostate cancer. The studies covered a wide spectrum of different interventions ranging from educational and counselling sessions, to nurse-led interventions for care at home, and full interdisciplinary palliative care team involvement in care. Double-blinding was not possible, and loss to follow-up through death or deterioration was high. Individual studies were generally small and underpowered, and pooling of data to gain power was not possible because of the problem of heterogeneity of interventions. Concealment of randomisation was also problematic with only three studies overall rated 'high' for quality of concealment of treatment allocation schedule.[8][9][10]

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9.1.3 Summary

Men with metastatic prostate cancer should be referred for interdisciplinary palliative care to assist in symptom control and provide emotional, social and spiritual support. This support has been shown to relieve caregiver burden and assist families and carers in providing effective end-of-life care. The involvement of an interdisciplinary palliative care team can improve symptom control and assist in the emotional, spiritual and social wellbeing in patients with advanced cancer.

At any time in the course of the illness, a patient and his family may need support from a communitybased service or a hospital-based consultative team, or even assessment and management by an inpatient palliative care unit. Often palliative care services that work closely with oncology units will gain earlier referrals for pain and symptom management for their prostate cancer patients. The nature of prostate cancer and the age of onset often mean that other medical conditions and co-morbidities may well require the involvement of aged care and geriatric support services at this time as well.

These factors highlight the importance of continuing research to support palliative care in the management of prostate cancer. All health professionals involved in the care of men with metastatic prostate cancer should feel comfortable in initiating palliative care or in making an appropriate referral for specialist interdisciplinary palliative care.

As to how best discuss prognosis and end-of-life issues with the patient and his care-givers, please see *Clinical practice guidelines for communicating prognosis and end-of-life issues with adults in the advanced stages of a life-limiting illness, and their caregivers.*[11]

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9.2 Referral to specialist palliative care

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9.2.1 In men with advanced prostate cancer, what is the evidence that referral to specialist palliative care can assist in supporting a patient's decision making and treatment planning processes?

In relation to the role of specialist palliative care in supporting decision-making and treatment planning processes, there was Level II evidence that a coordinated palliative approach to care can improve quality-of-life measures and enhance satisfaction for men and their carers.[1][2][3][4] Engelhardt described a programme of co-ordinated care of advanced illness in which a significantly increased number of patients completed advance care plans (p=0.006).[3] Supporting patients' processes of decision-making and care planning is seen as an important aspect of the work of specialist palliative care services. Palliative care services in Australia are often engaged in promoting the use of advance care planning instruments legislated by states and territories and in the appointment of a nominated medical agent.

Palliative care question 1: In men with metastatic prostate cancer what is the evidence that referral to specialist palliative care can assist in supporting a patient's decision-making and treatment planning processes?

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9.2.2 Evidence summary and recommendations

Evidence summary	Level	References
There is evidence that the involvement of a specialist palliative care team or a coordinated palliative approach to care can improve satisfaction with care for patients with advanced cancer, as well as increase the frequency with which advance care plans are made. This finding can be generalised to men with metastatic prostate cancer.	II	[1], [2], [3], [4]

Evidence-based recommendation	Grade
Men with metastatic prostate cancer should be referred for specialist palliative care or a coordinated palliative approach to assist in advance care planning.	**C**

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9.2.4 Appendices

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9.3 Symptom control

9.3.1 In men with advanced prostate cancer, what is the evidence that referral to specialist palliative care can assist with symptom control?

There was evidence that interdisciplinary palliative care can improve symptom management and enhance the wellbeing of men with metastatic prostate cancer. As far as symptom control was concerned a study involving a home nursing intervention and one involving a structured multidisciplinary intervention showed improvement in overall symptom control.[1][2] Pain management was improved in two models of co-ordinated home care[3][4]as was the symptom of dyspnoea in a nurse-led intervention[5] and with involvement of a palliative medicine team [6] . Vomiting was less frequent and more effectively treated in a study of co-ordinated care for terminally ill cancer patients.[7] Palliative interventions were shown to improve overall quality of life of the patient[2] as well as emotional wellbeing and functioning[2][3] and spiritual wellbeing.[6]Social functioning, mental and general health and vitality were improved in terminally ill patients.8 Financial wellbeing was also improved in one study. [2]

The opinions of caregivers (family and informal carers) were sought in relation to the management of the patient's symptoms in several studies. Increased satisfaction with the patient's pain management was reported in one study[8][9][10], with improved caregiver satisfaction with services for symptom control shown in six studies.[3][11] [12][8][9][10][13][14][15]

Although studies failed to show consistent improvement in all domains of care, this may reflect the fact that 'usual care' is not equivalent to 'no care' and 'usual care' already incorporates many elements of palliative care. The improvements shown in symptom control emphasises the significant benefit of involving interdisciplinary palliative care in managing men with metastatic prostate cancer, for both the patient and family carers.

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9.3.3 Appendices

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9.4 Pain control

9.4.1 In men with advanced prostate cancer what palliative interventions (including use of analgesics and co-analgesics) can assist in pain control?

No randomised controlled trials dealing specifically with analgesia for prostate cancer patients were found. However a vast literature dealing with analgesic treatments for cancer pain was identified. A systematic review of this literature was beyond the scope of these guidelines. As a result it was not possible to develop specific recommendations for this question. There are consensus recommendations regarding cancer pain management based on best available evidence.[1][2] The recommendations highlight the importance of routine screening for the presence or absence of pain, followed by comprehensive pain assessment if pain is present.

Depending on pain severity and type, there is support for the use of non-steroidal anti-inflammatory drugs (NSAIDs) and paracetamol for bone pain, with titration of opioids if required. The importance of breakthrough opioid dosing for patients on long-acting opioids, and the concurrent use of laxatives, is also emphasised.

Neuropathic pain may require a different approach, with the early use of tricyclic antidepressants and anti-convulsants as well as possible use of steroids.

Concurrent use of palliative radiotherapy, where appropriate, is highlighted, but the role of bisphosphonates in prostate cancer pain management remains uncertain (refer to evidence for the use of bisphosphonates in the prevention of skeletal events and evidence for the use of bisphosphonates in the treatement of bone pain). Following successful use of radiotherapy to control pain, analgesic regimens may require re-adjusting with continuing regular reassessment to reduce opioid use and prevent opioid accumulation and potentiation of opioid side-effects.

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9.4.3 Appendices

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9.5 Fatigue

Contents

9.5.1 In men with advanced prostate cancer, what interventions may ameliorate or minimise the symptoms of fatigue?

Fatigue remains the most prevalent symptom in patients with advanced cancer.[1] Fatigue in this setting is defined as 'An unusual, persistent, subjective sense of tiredness related to cancer or cancer treatment that interferes with usual functioning'.[2] A feature of fatigue in advanced cancer is that it is not relieved by rest or sleep.

In men with metastatic prostate cancer and extensive bone involvement with metastatic disease, fatigue may be secondary to anaemia due to bone marrow failure. If red cell transfusion is undertaken, it should be seen as a trial of therapy, where relief of fatigue rather than correction of blood figures should be the aim of the therapy.

In men receiving hormone therapy, a randomised controlled trial has shown that resistance exercise can reduce fatigue.[3] There is now a significant literature dealing with interventions, including exercise, for cancer-related fatigue. It includes two recent systematic reviews.[4][5] Many of the studies covered in these reviews did not include prostate cancer patients and were complicated by differing or unclear disease stages and continuing treatments that may not be applicable to prostate cancer patients. As a result it was not possible to develop specific recommendations about interventions that may ameliorate or minimise the symptoms of fatigue in men with more metastatic prostate cancer.

Palliative care question 2: In men with metastatic prostate cancer what is the evidence that referral to specialist palliative care can assist in symptom control?

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9.5.2 Evidence summary and recommendations

Evidence summary	Level	References
There is evidence that coordinated interdisciplinary palliative care can improve symptom management and emotional, spiritual and social wellbeing in patients with advanced cancer. This finding can be generalised to men with metastatic prostate cancer.	II	[6], [7], [8], [9], [10], [11]

Evidence-based recommendation
Men with metastatic prostate cancer should be referred for interdisciplinary palliative care to assist in symptom control and in providing emotional, social and spiritual support.

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9.6 End of life care

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9.6.1 In men with advanced prostate cancer, what is the evidence that specialist palliative care can assist patients and families in providing effective end of life care?

Specialist palliative care services were also shown to assist patients and their families in providing effective end-of-life care. A reduction in the number of hospital admissions was seen in one study[1] and is of particular relevance because it occurred in a population of nursing home residents where hospital avoidance would be an aim of palliative management. A reduction in time spent in hospital was shown in several studies.[2][3][1][4][5] Although death at home is often regarded as a desired outcome for palliative care interventions, only two of nine studies[6],[7][8][9] showed a significant increase in deaths at home. In Jordhøy[7], time at home was not significantly increased, but time spent in a nursing home in the last month of life was reduced. In a second study that related to a nursing home population there was also no significant difference in the proportion of carers who believed that then patient died where he/she wanted to.[1]

The increase in the number of patients completing advance care plans was taken as evidence of preparation for death[10], as was the increase in the number of patients who completed funeral arrangements.[11]

Informal or family caregivers derived significant benefit from the involvement of palliative care services in terms of their satisfaction with the care delivered, improvement in communication and their own improved quality of life.

Caregivers expressed increased satisfaction with quality of care.[12][2] [13][7][8][9][1][14][15] Hughes[12] reported an increase in satisfaction in relation to access to care and the technical quality, interpersonal elements and outcomes of care. Kane[2] [14] also found that carers reported better interaction with professionals and greater satisfaction with their own involvement in care. Ringdal[9] and Jordhøy[7] identified caregiver satisfaction with the availability of doctors to the family. This study also identified significantly improved satisfaction with a number of aspects of the information carers were given about the patient's prognosis and progress. Increased satisfaction with communication was also identified by Hughes[12] and SUPPORT.[16]

Where 24-hour practical nursing care in the home (hospital in the home) was compared with usual home care by a GP and district nurse[17], significantly more unmet need for night nursing support and for support for the carer in looking after the patient was identified in the control group. A study on the impact of an intervention in caregivers' coping skills showed a reduction in both task burden and the burden of the patients' symptoms for carers.[18]

However in one study[13], caregiver morale was lower in carers whose relative survived more than 30 days after discharge from hospital. This may reflect the continuing burden of caring when the expectation was for a short terminal illness.

A significant finding was an improvement in carers' overall quality of life[12][18] with Hughes[12] finding improvement in several specific domains relating to quality of life, including physical function, physical and emotional aspects of role function, mental health and social function. Addington-Hall[3] and Raftery[5] identified a decrease in caregiver expression of anger at the thought of the patient's death.

Provision of end-of-life care is a significant burden for informal caregivers. The evidence suggests this burden can be reduced through adequate provision of palliative care services, leading to improved outcomes for the family. This has the potential to have a major impact given the size of the population.

Palliative Care Question 3. In men with metastatic prostate cancer what is the evidence that specialist palliative care can assist patients and families in providing effective end of life care?

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9.6.2 Evidence summary and recommendations

Evidence summary	Level	References
In men with metastatic prostate cancer there is evidence that coordinated interdisciplinary palliative care can assist patients and families in providing effective end-of-life care, with more time spent out of hospital and reduction in the burden of providing care.	II	[12], [6], [18], [2], [10], [13], [17], [11], [3], [7], [8], [9], [1], [14], [15], [5], [16]

Evidence-based recommendation	Grade
Men with metastatic prostate cancer and their families should be referred for a coordinated palliative approach to assist in providing effective end of life care.	**C**

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10 Complementary and alternative therapies

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10.1 Complementary and alternative (unproven) therapies

Complementary medicine

Complementary medicine is any intervention that is used in conjunction with standard western health practices.

Integrative medicine

Integrative medicine is an approach that combines standard western health interventions and evidence based complementary medicines.

For example: the use of a course of relaxation therapy in conjunction with standard radiotherapy or chemotherapy regime to reduce stress anxiety.

Alternative medicine

Alternative medicine is an intervention or product offered as an alternative treatment to standard western medical practices.

(Source: Clinical Oncological Society of Australia CAM Definitions www.cosa.org.au)

The use of complementary and alternative (or unproven) medicine (CAM) has continued to increase. In 2004 it was reported that 52.2% of the Australian population used CAM.[1] In North America the reported prevalence of CAM usage in prostate cancer lies between 18 and 45%.[2] It is important that clinicians know about their patient's current and proposed CAM use as some CAM therapies can interfere with other therapies. However, a survey of patients using both conventional and complementary therapies found that many patients do not inform their doctor of their CAM use because they were not asked and because they did not see it important for the doctor to know.[3] To gain a comprehensive picture of CAM use and thus avoid possible adverse interactions it is important that all patients be carefully questioned as to their current or proposed usage of CAM agents in a supportive, understanding and non-judgmental way.[4][5] Schofield et al[5] provides recommendations and suggestions on how to discuss CAM usage. Their systematic review revealed that there is no level IV or higher evidence for communicating about CAM with cancer patients. As a result their recommendations are based on a systematic review of descriptive studies of, a review of generic communication skills and expert opinion.

Evidence-based recommendation	Grade
Health professionals should ask their patients about their use of CAM therapies in a supportive, understanding and non-judgmental way.	**D**

While there have been numerous reports on the level of CAM usage in men with prostate cancer, there are limited studies on the factors motivating them to use it. One study[2]hypothesised that users of CAM did not assess conventional and non-conventional treatments in the same way as non-users. CAM users perceived CAM to be safer than conventional treatments and showed greater concern for side effects of conventional therapy such as impotence. Non-users of CAM questioned its validity, perceived conventional care as 'curing' cancer and were more accepting of possible side effects such as impotence and secondary cancers. They had more definite views on the benefits flowing from conventional medicine and trusted their doctors more fully.

A prospective study[6] involving 111 men noted that those who used CAM were more uncertain about prostate cancer and its treatment than men who chose to follow the conventional therapy route. However it was noted that CAM users were less distressed than non-users after a year of treatment.

In general there are two large areas of therapy for advanced prostate cancer under the CAM umbrella:

- touch therapies (eg Reiki, massage, acupuncture and mind–body interventions)
- dietary interventions (eg dietary modifications, vitamin and herbal supplements).

There are no randomised controlled trials (RCTs) examining the benefit of touch therapies in prostate cancer and so these are not discussed further in this chapter.

A wide range of products has been offered for the treatment of prostate cancer. While there is an increasing number of RCTs investigating the use of dietary interventions for treating cancer, the general rigour of such trials is frequently deficient or of poor quality. This feature, however, is not limited to CAM studies.[7] Quality of life was not measured formally in any of the studies found. The following summary describes the RCTs that met the criteria for inclusion in these guidelines.

Only four dietary interventions have been subjected to RCTs that were completed and were not part of a chemotherapy-centred regimen. (see also section 2.3 Effect of diet and lifestyle interventions on quality of life, p7) CAMs showing potential were high-dose vitamin D (calcitriol), lycopene, ellagic acid, and the dietary supplement verum. Lycopene is a carotenoid and is claimed to be a quencher of free radicals and an immunomodulator. Ellagic acid, a polyphenol extracted from Punica Granatum (pomegranate) seeds may have pro-apoptotic and anti-oxidant properties. Verum is a dietary supplement that contains selenium, carotenoids and other putative prostate cancer inhibitors.

The role of vitamin D in treating cancer is not fully understood. It may block cancer cell proliferation or improve immune system function, however, further research is needed to clarify this association. Folinic acid forms part of some chemotherapy regimens and therefore is not included under CAM.

Another trial[8] was planned to evaluate the efficiency of PC-SPECS, a herbal conglomerate, with that of diethylstilbestrol (DES) in a crossover study in patients with androgen-independent prostate cancer. This study was discontinued because the researchers found traces of DES in four samples of PCSPECS. Further studies by the California Department of Health found contamination with warfarin, alprazolam and DES. These observations highlight the need for investigators to ensure the purity of herbal cocktails they are using.

In a small, low powered study, Ansari et al compared lycopene with orchidectomy against orchidectomy alone among 54 patients with advanced prostate cancer.[9] Patients in the lycopene and orchidectomy arm had a statistically significant increased survival as compared with the group who had orchidectomy alone ($p<0.001$). Progression was measured by reviewing new ‘hot spots’ on bone scans or any increase over the initial PSA by 25%. Follow-up bone scans revealed four patients (15%) in the orchidectomy-only group had a complete response compared with eight (30%) in the orchidectomy plus lycopene group ($p<0.02$). PSA level was not statistically different at six months, but at two years the orchidectomy plus lycopene group achieved better PSA response compared with those who had orchidectomy only (78% versus 41%, $p<0.001$). Pain response was measured through analgesic intake. There was a linear response to treatment in relation to daily requirements for analgesics. When complete response was observed on bone scans, no analgesic requirement was observed in either group. However, the group taking lycopene had more patients who did not require analgesics than the group having orchidectomy alone (25% versus 15%, p value not reported). There was also a statistically significant improvement in peak urine flow rates in the lycopene group with acorresponding benefit in obstructive symptoms ($p<0.04$). The result of this small study would appear to encourage further investigation of lycopene in the management of advanced prostate cancer.

Studies on vitamin D revealed conflicting results. One showed a benefit for survival and the other found excess deaths in patients receiving vitamin D supplements. Reddy et al[10] examined the use of high-dose vitamin D supplements in combination with weekly docetaxel versus docetaxel alone in 250 patients with metastatic androgen-independent prostate cancer. The combination treatment resulted in significantly better survival, with a 33% (95% confidence interval:0 3 to 55%) relative reduction in risk of death in this group (median survival 23.5 months versus 16.4 months, $p=0.04$). Vitamin D supplementation was observed to increase the duration of

freedom from skeletal morbidity, although not significantly.[10][11] The time to a PSA response, tumour response rate and proportion of patients with a PSA decrease of at least 50% were not significantly different. Overall, patients in the vitamin D and docetaxel arm suffered fewer side effects than the docetaxel alone group (27% versus 41%, p=0.05). Noticeably, the rate of thrombotic events was lower in the vitamin D arm (2% versus 9%, p=0.02). However the risk of myelosuppression and infection rates was not significantly different. A larger trial comparing the combination of calcitriol and docetaxel with docetaxel alone was terminated in the United States of America because of excess deaths in the calcitriol arm (NCT 0027333, RCT, USA). This illustrates the need for all studies to be published, no matter the outcome of the results or whether they were terminated early due to safety concerns.[12] The difficulty or happenstance in accessing readily available information in trials 'gone wrong' is a concern.

The addition of ellagic acid to estramustine and vinorelbine did not significantly improve survival among 48 consecutive patients with hormone-resistant prostate cancer in a study by Falsaperla et al.[13] The proportion of patients in the ellagic acid group with a complete or partial PSA response was higher, and fewer had progressive disease (p=0.03). Analgesic use decreased more in the ellagic acid group (75% versus 42%, p=0.04). There were no significant differences in PSA decrease, and the significance level for duration of pain response was not reported. There were no significant differences in the rate of grade 3 or 4 toxicity in the ellagic acid group except for anorexia, where the rate was lower. It should be noted that ellagic acid is not presently available in Australia.

Kranse et al[14] conducted a double-blind randomised placebo-controlled two-arm cross-over intervention study of the dietary supplement, verum, in 37 prostate cancer patients with no systemic treatment and a rising PSA. The study measured the rate of change of serum concentration of total and free PSA and serum levels of male sex hormones dihydrotestosterone and testosterone. While total PSA doubling time was unaffected, free PSA increased during the placebo phase and decreased during the verum phase (p=0.02). A significant decrease in both total and free PSA was observed (p=0.04) in 21 of 32 men in whom the free androgen index decreased. Survival, toxicity and pain were not reported in this study and there was no significant effect on disease progression.

A recent systematic review of dietary prevention and treatment of prostate cancer advises that doctors must ensure that excessive amounts of dietary supplements should be avoided as adverse events may follow such consumption.[15]

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10.2 Evidence summary and recommendations

Evidence summary	Level	References
A small single RCT found lycopene in addition to orchidectomy has been demonstrated to improve survival, decrease progression and result in better PSA response than orchidectomy alone.	II	[9]
There are contrasting results from two studies on the benefit of vitamin D (calcitriol), with one reporting a survival benefit and the other being terminated due to excess	II	[10], [12]

Evidence summary	Level	References
deaths in the calcitriol group.		
The dietary supplement, verum, may decrease free PSA levels and androgen levels.	II	[14]
There is no clear benefit from vitamin D, lycopene or verum in relation to pain relief.	II	[9], [10]
There is a paucity of information on the toxicity of dietary supplements in advanced prostate cancer.	II	[9], [10], [14]

Evidence-based recommendation	Grade
Calcitriol in combination with docetaxel chemotherapy is not recommended on the basis of a large randomised trial which found excess mortality.	**A**

Evidence-based recommendation	Grade
Lycopene may benefit a small group of men with metastatic prostate cancer who have had no radiotherapy, no hormone therapy and who have had orchidectomy. In view of these findings, lycopene deserves to be further trialled.	**C**

Evidence-based recommendation	Grade
There is insufficient evidence to make any recommendations on dietary supplements in relation to quality of life, pain relief and toxicity.	**C**

For those requiring a broader review of complementary medicines, there was a National Prescribing Service (NPS) Review in March 2009. (NPS is an independent non-profit organisation for quality use of medicines and is funded by the Australian Government Department of Health and Ageing.)[16]

Also refer to: Memorial Sloan-Kettering Cancer Center for cancer information about herbs, botanicals and other products at http://www.mskcc.org

"Understanding Complementary Therapies: A guide for people with cancer, their families and friends", Cancer Council New South Wales October 2008 at www.cancercouncil.com.au

Advanced Prostate Cancer: A guide for men and their families. Australian Prostate Cancer Collaboration, Australian Cancer Network. 2009. In press

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11 Socio-economic aspects of advanced prostate cancer

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11.1 Socio-economic aspects of advanced prostate cancer

Adverse social and economic circumstances are well-recognised determinants of access to and use of health care. Less affluent or socially disadvantaged people live shorter lives and suffer more illness than those who are well off.[1]Guideline development needs to consider how issues such as income, education, occupation or employment, ethnicity, indigenous status, literacy, and place of residence affect risk factors, use of health care services and outcomes of care. There is growing evidence that socio-economic status (SES) is associated with prostate cancer outcomes, particularly participation in PSA testing, patterns of care for localised disease and with survival and mortality outcomes. Most of this evidence is based on American or European studies. Randomised controlled trials rarely report whether trial selection is associated with social class or whether interventions for advanced prostate cancer are confounded by SES. The relationships between SES and prostate cancer incidence, mortality and survival in Australia are poorly understood and even less is known about the association between SES and advanced prostate cancer.

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11.1.1 Socio-economic status

A number of studies have demonstrated a higher risk of diagnosis of prostate cancer in men from higher SES groups. This is likely to be related to higher prevalence of prostate cancer testing in those with higher education, income and health-seeking behaviours. In New South Wales between 2002 and 2006, the incidence of prostate cancer was 15% higher than average in men resident in the highest socio-economic status areas, compared to an 8% lower risk in the lowest SES group. However there was no significant difference in mortality rates by SES groups.[2] Hall, using linked administrative data from Western Australia, found higher three-year mortality from prostate cancer in more socioeconomically disadvantaged groups (relative risk=1.34, 95% CI=1. 10 to 1.64), whereas those admitted to a private hospital (relative risk=0.77, 95% CI=0.71 to 0.84) or with private health insurance (relative risk=0.82, 95% CI=0.76 to 0.89) fared better.[3] International studies have shown that men with localised disease with lower incomes are less likely to be treated at all, and if treated for localised cancer they are less likely to have prostatectomy and more likely to have radiation therapy.[4][5]A number of studies have shown that men with higher incomes and private health insurance status are more likely to have aggressive treatment, better quality of life and lower mortality from prostate cancer.[6][7][8][9] The role of income, education and health insurance in the determination of advanced prostate cancer outcomes in Australia has never been explored.

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11.1.2 Accessibility

Coory and Baade10, using administrative data for the whole of Australia, found a statistically significant and increasing excess risk for prostate cancer mortality in regional and rural areas. In 2000–2002, the excess (compared with capital cities) was 21% (95% CI=14% to 29%). The authors suggested that this was likely related to lower rates of screening with PSA tests and treatment with radical prostatectomy in rural and regional Australia.[10]Western Australia data indicate that the three-year mortality rate for prostate cancer was greater with a first admission to a rural hospital (relative risk=1.22, 95% CI=1.09 to 1.36) compared to non-rural

hospitals.[3] A survival analysis comparing rural and remote residents of NSW found a more than three-fold relative excess risk of death by five years in men from rural and remote NSW (relative risk=3.38, 95% CI=2.21 to 5.16). This was partly driven by later stage of disease at diagnosis in men from rural and remote areas.[11] An analysis of linked data for NSW for the period 1993–2002 also showed associations between SES and rural/urban areas of residence and the type of treatment received. Prostate cancer patients from less accessible areas of the state were more likely to have orchidectomy than those from accessible areas and men from more socially disadvantaged areas also had higher rates of orchidectomy.[12]The most recent data continue to show the incidence gradient in risk of all prostate cancer by rural and urban status but indicate that the inequity in mortality may have declined. Data from the NSW Central Cancer Registry show that men in rural areas had 28% (95% CI=9% to 49%) higher than expected incidence of prostate cancer but no significant difference in mortality.[2]

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11.1.3 Indigenous groups

Indigenous Australians have lower risk of diagnosis of prostate cancer compared to non-indigenous Australians.[13]The prostate cancer mortality rate ratio for indigenous males from the Northern Territory was 0.4 (95% CI=0.2 to 0.8), indicating lower risk of death from prostate cancer in indigenous Australians.[14]

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11.1.4 Ethnicity and race

Black men have the highest incidence and mortality rates from prostate cancer worldwide. In a systematic review of 29 studies in the USA, 79% observed no difference in treatment outcomes in black men after controlling for tumour and patient characteristics. Although several studies have focussed on outcomes in men with locally advanced[15] or metastatic prostate cancer[16] and showed worse outcomes in black men, other studies of metastatic cancer did not find evidence of black–white differences in all cause or prostate cancer survival.[17] In a study of 1183 men with hormone-refractory prostate cancer from eight multicentre trials, race had no effect on the median survival time of blacks compared with whites (hazard ratio 0.85, 95% CI=0.71 to 1.02, p=0.08).[18] Observational studies have demonstrated that much of the racial difference in survival from prostate cancer is confounded by black men's younger age at diagnosis, more distant stage, higher tumour grades, less aggressive treatment and lower SES[19][20] while others dispute whether race is associated with survival per se.[21] Australian men born in other countries generally have lower risk of developing prostate cancer and of dying from it than Australian-born males, but higher risk of developing prostate cancer than reported in their native countries.[22] Whether ethnic differences in men's willingness to access screening and treatment for prostate cancer in Australia follows through into differences in treatment for men with advanced prostate cancer is unknown.[23][24]

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11.1.5 Literacy and language ability

Poor literacy in USA populations is associated with advanced-stage prostate cancer and has been linked to increased prostate cancer mortality.[25][26] Low literacy levels likely result in complex interactions in the communications between care givers and patients regarding compliance with treatment, treatment outcomes and the decision-making process.[27] A systematic review of decision making in patients with advanced cancer showed active decision making was less common in men with prostate cancer than in women with breast cancer. A number of simple interventions including question prompt sheets, audio-taping of consultations and patient decision aids have been shown to facilitate increased involvement in decision making.[28]

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11.1.6 Social support

An RCT in the USA of men with metastatic prostate cancer indicated that a lack of social support for single males potentially led to earlier re-treatment rates and concluded this was partly due to inadequate social support in receiving additional care.[29] Two Australian surveys of the supportive care needs of men with prostate cancer (irrespective of stage) have shown higher levels of unmet needs in men with lower income or lower levels of education.[30][31]

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11.1.7 Socio-economic status and involvement in randomised controlled trials

Participants in randomised controlled trials, the source of the evidence predominantly used to inform the recommendations in these guidelines, may not fully represent economically or socially disadvantaged sub-populations because of lower participation by these groups in trials.[32]Whether this affects the ability to generalise the results from these trials is seldom reported. Several of the larger population-wide randomised controlled trials of prostate cancer screening and treatment have identified socio-economic differences in race, income and occupation between participants and nonparticipants. [33][34][35][36] Similarly, men with chronic disabilities are significantly less likely to participate in prostate cancer prevention trials.[37]

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11.1.8 Socio-economic status implications for these guidelines

Understanding the precise role of SES in relation to advanced prostate cancer outcomes is a key challenge for future research. There is a lack of clear evidence from either international studies or local surveys of advanced prostate cancer patients to indicate that inequity in outcomes is associated with social or economic resources of patients. However, by extending the evidence from studies of access to care for localised prostate cancer, it would appear that certain groups may be at risk of inequitable care, including socially or regionally isolated men and those without the means or education to find and purchase the best level of care.

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11.2 Evidence summary and recommendations

Evidence-based recommendation	Grade
Based on a lack of evidence from randomised trials or observational studies, it is not possible to determine whether socio-economic status is associated with differences in outcomes for men with locally advanced or metastatic prostate cancer.	**D**

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12 Emerging therapies

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12.1 Emerging therapies

It is impossible to undertake a comprehensive review of all published material in the development of any set of guidelines. However it seemed useful to add an appendix to these guidelines for reference by clinicians looking for outcomes of randomised control trials in the management of locally advanced and metastatic prostate cancer. The therapies itemised were therapies for advanced or metastatic prostate cancer currently being studied in randomised controlled trials. The National Institute of Health (NIH) registry[1]website and the World Health Organization (WHO) primary and partner registries[2](found at www.who.int/ictp/network) were searched for randomised controlled phase III trials of treatments for advanced prostate cancer which were ongoing (trial registry updated 2000 or onwards). These registries included the National Cancer Institute's Physician Data Query cancer clinical trials registry (www.cancer.gov) and the Australian New Zealand Clinical Trials Registry (www.anzctr.org.au). Readers are referred to these two registries for details of ongoing clinical trials for prostate cancer treatments that are recruiting in Australia.. Trials described as complete were checked for publications and trials described as terminated were checked where possible for the reasons they were terminated. Trials with mature data included in the systematic reviews or their appendices were not included. It should be noted that in most cases this summary depends on the information provided by the trial register, which is not always accurate, clear or current, and thus it is not a comprehensive review.

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12.1.1 For men with locally advanced disease

There are numerous continuing trials examining different radiotherapy techniques, including intensity modulated radiotherapy (IMRT) and hypofractionation, dose escalation, and the addition of radiotherapy to hormone therapy and to brachytherapy. Similarly, there are numerous trials examining different regimens and types of hormone therapy as a monotherapy, as an adjuvant or neo-adjuvant to definitive therapy, and as an addition to adjuvant radiotherapy. There are also continuing trials examining docetaxel as an adjuvant to definitive therapy with or without hormone therapy, and one study currently recruiting patients for a trial of chemohormonal therapy as a neoadjuvant to prostatectomy. In contrast, only two trials were identified that examined surgery (prostatectomy and cryoablation) and it is unclear whether they include men with locally advanced disease. There are at least two trials that appear to be ongoing, which are examining the effects of zoledronic acid. A trial is planned to assess the effect of a multidisciplinary support program for patients undergoing definitive radiotherapy and a trial has been completed of the isoflavenoid genistein. For men on hormone therapy there are at least four trials testing various exercise regimens as well as a trial of green tea extract.

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12.1.2 For men with biochemical relapse following definitive therapy

There are at least two trials examining salvage radiotherapy; numerous trials examining various hormone therapy modalities and regimens, including immediate versus delayed; and at least three trials examining chemotherapy, including docetaxel, as an adjuvant to hormone therapy. Thalidomide and rosiglitazone are also being studied. In addition, several dietary interventions are being trialled, including pomegranate juice, lycopene with vitamin E, and an intensive nutritional intervention focusing on a low-fat diet high in fibre, fruit, vegetable, green tea and vitamin E.

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12.1.3 For men with metastatic disease

There are numerous trials studying the addition of bisphosphonates, primarily zoledronic acid, to hormone therapy. There are trials examining various hormone therapy regimens and modalities and the addition of doctaxel to hormone therapy. One trial is examining the benefits of prostate radiotherapy in addition to hormone therapy for men diagnosed with metastatic prostate cancer. For painful bone metastases, the bisphosphonate ibandronate is being studied as alternative to or in addition to radiotherapy. For spinal metastases with microfractures or compression fractures, vertebroplasty is being studied as an addition to radiotherapy. A trial of suramin in addition to hormone therapy has been completed. Suramin is a molecule that interferes with the action of a number of growth factors, including those involved in angiogenesis.

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12.1.4 For men with castrate-resistant prostate cancer

For men with castrate-resistant prostate cancer without clinical evidence of metastases, docetaxel chemotherapy and endothelin-A receptor antagonists atrasentan and zibotentan (ZD4054) are being trialled. These patients may also be included in continuing trials for the treatment of castrate-resistant or hormone refractory prostate cancer with abiraterone, which blocks testosterone synthesis; diethylstilbestrol; the bisphosphonate risedronate; the RANK ligand antibody denosumab; the PDGFR inhibitor leflunomide; and a peptide vaccine. A trial of immediate versus delayed psychological intervention for patients with advanced cancer has been completed.

For men with castrate-resistant prostate cancer with metastases there are continuing trials of the bonetargeting radioisotope radium-223; the addition of strontium 89 to docetaxel chemotherapy; the addition of zoledronic acid to standard therapy; dexamethasone regimens; the taxoid XPR6258; doxorubicin; endothelin A antagonists atrasentan and zibotentan (ZD4054); sunitinib, a receptor kinase inhibitor, aflibercept and bevacizumab, which target VEGF, which drives angiogenesis: prinomastat, which inhibits matrix metalloproteases involved in tumour invasion, angiogenesis and metastasis; and Provenge, dendritic stem cell precursors activated by exposure to prostatic acid phosphatase. The GVax prostate vaccine trials have been terminated due to an imbalance of deaths. Finally, there is a continuing trial of Auron Misheil Therapy 2003, a combination of camomile extract calcium, vitamins, anti-histamine and insulin.

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12.3 Appendices

View initial literature search

12.1 Guideline development process

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12.1.1 Guideline development process

12.1.1.1 Introduction

The Australian Cancer Network (ACN) initiated a proposal to develop the Clinical practice guidelines or the management of advanced prostate cancer. A decision to proceed was taken in September 2005. To better describe the scope of the guidelines, the title was changed to Clinical practice guidelines for the management of locally advanced and metastatic prostate cancer.

A Working Party composed of clinical specialists and consumers and a project team based in the Cancer Epidemiology Research Unit of Cancer Council New South Wales, carried out the work. The project team conducted literature searches, assisted in the critical evaluation of the literature and extracted the relevant data. Financial support was provided by Andrology Australia, the Prostate Cancer Foundation of Australia and ACN. NHMRC appointed a Guideline Assessment Reviewer (GAR) to both monitor and aid the development process.

The development program was designed to meet the scientific rigour required by the guideline development process, which is the subject of a series of handbooks on the main stages involved in the development of clinical practice guidelines.[1] [2][3][4][5][6][7][8]These handbooks have been previously condensed into a single volume—Development of clinical practice guidelines for the management of cutaneous melanoma and melanoma in special sites: a handbook for chapter leaders and expert working groups[9]—which outlines the major steps and expectations involved in developing guidelines and provided a clear path for everyone involved in the project. This handbook provides the definitions and protocols for developing research questions and search strategies, conducting searches and critical appraisal, summarising and assessing the relevant literature and finally, formulating the recommendations. It includes checklists and templates created to satisfy designated standards of quality and process. These condensed handbooks have been a most useful aid in the demanding and, for some, new process of developing guidelines.

At its initial meetings the Guidelines Working Party prepared a table of topics and developed questions to address identified clinical needs. The questions were divided into different topics and subcommittees of the Guidelines Working Party were formed to address topics in their areas of expertise

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12.1.1.2 Steps in preparing clinical practice guidelines to NHMRC criteria

A clear strategy was developed for every topic and each expert group followed the appropriate steps in preparing the guidelines. While each subcommittee received significant assistance from the project team skilled in methodology, the subcommittees themselves oversaw the synthesis of the evidence and formulation of the recommendations for their topics.

The strategic steps followed are outlined below:

1. Structure the research questions

2. Develop a search strategy

3. Search the literature

4. Select, assess and summarise the literature

5. Critically appraise and summarise each selected article

6. Assess the body of evidence and formulate recommendations

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12.1.1.3 Structure the research questions

A wide range of questions was proposed for research. The questions focussed on interventions rather than diagnosis or prognosis. All proposed questions were reviewed on the basis of their purpose, scope and clinical importance to the target audience and were structured according to the PICO (populations, interventions, comparisons, outcomes) formulation.

The questions were ranked and then 52 were identified as requiring systematic reviews.

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12.1.1.4 Develop a search strategy

Each research question was submitted to a search strategy based on the PICO formulation. Most searches were directed to prostate cancer as a generic base. Searches were limited or widened as necessary, but all maintained the PICO structure. Keywords were selected during the PICO process. Further sources for keywords or MESH and subject terms were derived from evidence-based material, systematically reviewed articles and appropriately relevant literature. A single systematic search strategy was derived from these terms and applied to all included electronic databases.

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12.1.1.5 Search the literature

Clinical practice guidelines should be based on systematic identification and synthesis of the best available scientific evidence.[1] All literature searches were conducted systematically using electronic databases concluding 1 April 2006. Examples include:

- *Medline*: bibliographic references and abstracts to articles in a range of languages on topics such as clinical medical information and biomedicine, and including the allied health fields, biological and physical sciences
- *EMBASE*: major pharmacological and biomedical database indexing drug information from 4550 journals published in 70 countries
- *Cinahl*: bibliographic references and abstracts to journal articles, book chapters, pamphlets, audiovisual materials, software, dissertations, critical paths, and research instruments on topics including nursing and allied health, biomedicine, consumer health, health sciences librarianship, behavioural sciences, management, and education
- *Cochrane* Library: regularly updated collection of evidence-based medicine databases, including The Cochrane Database of Systematic Reviews
- *Clinical evidence*: compendium of evidence on the effects of clinical interventions updated every six months published by the British Medical Journal Publishing Group
- *Psychinfo*: Bibliographic references and abstracts to journal articles, book chapters, dissertations and technical reports on psychology; social, clinical, cognitive and neuropsychology; psychiatry, sociology, anthropology and education, with source material from a wide range of languages.

For each search, the following details were provided in topic- or question-specific reports (available on request from the Australian Cancer Network):

- electronic databases searched
- terms used to search the databases
- search inclusion or exclusion criteria
- language
- study type

Studies published before 1 April 2006 could be included in the systematic reviews. Studies published after this date could not be included in the evidence base for the recommendations but could be referred to in the text and were described in the Appendices to the topic- or question-specific reports (available on request from the Australian Cancer Network). The project team also hand-searched the reference lists of the relevant articles to identify additional articles that had not been detected through searches of the electronic databases. Bi-annual meetings of the guidelines Working Party provided a forum for discussing and sharing overlapping evidence, the discovery of unpublished literature and information from other key organisations or individuals.

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12.1.1.6 Select, assess and summarise the literature

The literature identified by the electronic database searches was assessed for relevance to each question. The following steps were taken to select and sort the literature, with the details and results summarised in topic- or question-specific reports (available on request from the Australian Cancer Network):

1. Define the inclusion criteria

2. Review titles and abstracts of retrieved citations to identify potentially relevant articles

3. Obtain the full text of potentially relevant articles

4. Determine whether the study described in each collected article met the pre-defined inclusion criteria

5. Determine whether systematic reviews accounted for all preceding literature

6. Prepare folders to file searches, background papers and reviewed articles for each question addressed

Two independent assessors then assessed the quality of each of the included studies according to predefined criteria for the various study types. Any disagreements were adjudicated by a third reviewer.

The quality criteria were:

- *randomised controlled trials (RCTs)*: blinding, allocation concealment, follow up and intentionto- treat analysis and mode of randomisation
- *systematic reviews*: search strategy used, the inclusion criteria and their application, study quality assessment, summary descriptive tables, pooling methods and examination of heterogeneity
- *quasi-randomised and cohort studies*: subject selection, group comparability, comparability of outcome measurement, blinding and completeness of follow up. Criteria for the critical appraisal process are available on the Australian Cancer Network website (<www.cancer.org.au/acn>). Summaries of the studies were tabulated in PICO format and the relevant data extracted and summarised in tables. The data extraction was checked by a second assessor. These tables of study haracteristics and evidence are included in the topic- or question-specific reports (available on equest from the Australian Cancer Network). The reports also contain lists of collected studies that dd not meet the inclusion criteria and the reason for their exclusion.

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12.1.1.7 Critical appraisal and summary

For each clinical question, the included studies and their results were summarised in a template (Template 1 in the Handbook[9]). Each study was submitted to further critical appraisal. The level of the evidence, the quality of evidence as determined above, the size of effect and relevance of the evidence of each included study was documented.

Details of the templates, rating systems, and criteria for the critical appraisal process are available on the Australian Cancer Network website (<www.cancer.org.au/acn>). Levels of evidence are outlined below.

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'**Designations of levels of evidence for intervention research questions (NHMRC, 2005)**

Level	Intervention
I	A systematic review of level II studies
II	A randomised controlled trial
III-1	A pseudo-randomised controlled trial (ie alternate allocation or some other method)
III-2	A comparative study with concurrent controls: • non-randomised, experimental trial • cohort study • case-control study • interrupted time series with a control group
III-3	A comparative study without concurrent controls: • historical control study • two or more single-arm studies • interrupted time series without a parallel control group
IV	Case series with either post-test or pre-test/post-test outcomes

Source: Development of clinical practice guidelines for the management of cutaneous melanoma and melanoma in special sites: Handbook for chapter leaders and expert working groups[9], p18

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12.1.1.8 Assess the body of evidence and formulate recommendations

The body of literature was assessed by each expert sub-committee in regard to the volume of the evidence, its consistency, clinical impact, generalisability and applicability. These aspects were graded and documented in a second template (Template 2 in the Handbook[9]).

Following grading of the body of evidence, expert sub-committees were asked to formulate a recommendation that related to the summarised body of evidence. This recommendation also had to be graded as follows:

Grade of Recommendation	Description
A	Body of evidence can be trusted to guide practice

Grade of Recommendation	Description
B	Body of evidence can be trusted to guide practice in most situations
C	Body of evidence provides some support for recommendations but care should be taken in its application.
D	Body of evidence is weak and recommendation must be applied with caution

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12.1.1.9 Writing the chapter

All the expert sub-committees were asked to write their guidelines chapter using the following format:

- background
- review of the evidence
- evidence summary with levels of evidence and numbered references
- recommendation(s) and corresponding grade(s)
- references

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12.1.1.10 Review of the chapters

The body of evidence and recommendations for each chapter were reviewed by the Guidelines Working Party and final recommendations agreed to, based on the evidence.

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12.1.1.11 Public consultation

A complete draft of the guidelines was sent out for public consultation in Australia in September 2009. The consultation process included soliciting public review of the document through advertisement in a national newspaper, and alerting professional societies and groups and sponsors. All feedback on the draft received during the consultation period in Australia was reviewed by the Guidelines Working Party. Subsequent changes to the draft were agreed by consensus, based on consideration of the evidence. A final independent review of experts in their fields was conducted before the final draft was submitted for publication.

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12.1.1.12 Dissemination and implementation

The Australian Cancer Network will take the lead in disseminating the guidelines in Australia. This will include a campaign to raise awareness of the new guidelines that incorporates organised media coverage through multiple outlets and an official launch. The Guidelines will be distributed directly to relevant professional and other interested groups and through meetings, national conferences, and other CME events. A significant effort will be made to have the Guidelines introduced to senior undergraduate medical students and to encourage the relevant learned Colleges, which are usually binational (surgeons, radiation oncologists and pathologists), to support the Guidelines and to foster their integration into hospital and community practice through resident and registrar education activities.

The scope of implementation activities will depend on the availability of funding. Use of the Guidelines as part of core curriculum in specialty exams will be encouraged. It is recognised that a planned approach is necessary to overcome specific barriers to implementation in particular settings and to identify appropriate incentives to encourage uptake of guideline recommendations. Implementation of the Guidelines will require a combination of effective strategies and may include further CME initiatives and interactive learning, the development and promotion of computer-assisted decision aids and electronic decision-support systems, and the creation of audit and other clinical tools.

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12.1.1.13 Consumer feedback process for Consumer version of Clinical practice Guidelines

A consumer document has been produced and is in its implementation phase. To ensure strong consumer input into the development of the consumer version of the Guidelines, we worked in partnership with the Prostate Cancer Foundation of Australia (PCFA). This organisation has a network of over 80 peer support groups in each state and territory. All peer support groups involve families as well as men with prostate cancer.

The PCFA nominated support group members for the consumer guide committee. Two members with advanced prostate cancer, Mr Trevor Hunt and Mr Don Baumber were nominated initially, and made enormously helpful contributions in the early stages. As we approached the final stages of development, two additional peer support members, Mr Bill McHugh and Max Shub were also appointed. Bill is immediate past Chair of the Support and Advocacy Committee of the Prostate Cancer Foundation of Australia.

When the final draft of the Guide was ready for feedback, Bill McHugh and Max Shub organized a process, so that all support group members in all states and territories could provide feedback on a section (three chapters) of the Guide. Because the Guide was very long (250 pages), it was thought that this was the best way to get feedback on all chapters in the Guide, but not overburden men and their families with too much to read. Feedback was then compiled by two medical members of the PCFA support group network and forwarded to the committee. The revised document was then reviewed again by these members and our consumer representatives.

When the consumer guide was launched, presentations were organised in Sydney, Melbourne and Brisbane at a PCFA event featuring a visiting international speaker, medical oncologist and prostate cancer survivor Dr Charles “Snuffy” Meyers. All of these events were well attended (200 or more attendees), providing discussion and feedback. The Guide was also launched at the Urological Society of Australia and New Zealand’s annual meeting in February 2010.

Widespread distribution to Urologists and other clinicians has been initiated by Andrology Australia and there has been enthusiastic uptake at the practice level. The document is available for download from the four major organisations, which are sources of prostate cancer information nationally (Andrology Australia www.andrologyaustralia.org, Prostate Cancer Foundation of Australia www.pcfa.org.au, Cancer Council Australia www.cancer.org.au/clinicalguidelines, Lions Australian Prostate Cancer website www.prostatehealth.org.au).

The book has been welcomed by major consumer organisations.

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12.1.2 References

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12.2 Working party members and contributors

Contents

12.2.1 Working party members and contributors

Management of Metastatic Prostate Cancer Guidelines Working Party Membership

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Mr Don Baumber	Consumer -Gold Coast QLD
Professor Damien Bolton	Urologist - Melbourne VIC
A/Professor Mark Boughey	Palliative care specialist - Melbourne VIC
Dr Mary Brooksbank	AM Palliative care physician - Adelaide SA
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Ms Helen Crowe	Urological Nurse - Victorian Urological Nurses Society, Melbourne VIC

Professor David Currow*	Palliative care physician - Adelaide SA
Ms Melissa Dougherty*	Epidemiologist - Adelaide SA
Dr Joshua Dass	Radiation oncologist - Townsville QLD
Professor Gillian Duchesne**	Radiation oncologist - Melbourne VIC
Professor RA 'Frank' Gardiner AM	Urologist - Royal Brisbane and Women's Hospital, Brisbane QLD
Dr Kumar Gogna	Radiation oncologist - Mater Centre, Brisbane QLD
Dr Howard Gurney	Medical Oncologist - Westmead Hospital, Sydney NSW
Professor David Handelsman	Endocrinologist - ANZAC Research Institute, Sydney NSW
Mr Trevor Hunt	Consumer – Adelaide SA (deceased 22 June 2009)
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Mr Bill McHugh	Consumer – Brisbane QLD
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A/Professor Jeremy Millar***	Radiation oncologist – Alfred Hospital, Melbourne VIC
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12.2.1.2.5 Hormone therapy

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12.2.1.2.7 Palliative care

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12.2.1.2.8 Psychosocial care

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12.2.1.2.10 Socio-economic aspects

Dr David Smith

12.2.1.2.11 Surgery

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** Until 31 December 200

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12.2.1.2.12 Guidelines development process

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Dr Carole Pinnock AM
Mr Max Shub
Mr John Stubbs
Professor Jane Turner

In attendance:
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Ms Suzanne Hughes
Professor Dianne O'Connell
Emeritus Professor Tom Reeve AC CBE
Professor Villis Marshall AC

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12.2.1.3 Acknowledgments

Professor Madeleine King and Dr Tim Luckett for their input in the quality of life aspects of the hormone therapy sections.

Ms Hester Gascoigne of Hester Gascoigne & Associates, Canberra for editing the draft document for public consultation.

Ms Mary Russell, Freelance Indexer, Caulfield Victoria, for indexing the Guidelines.

Ms Christine Vuletich, Executive Assistant, Australian Cancer Network, for formatting Guidelines, layout and editing.

Yaping Liu, Librarian and Ying Zhao, Library technician at Cancer Council New South Wales, for helping collect references.

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12.3 TNM classification of prostate tumours

Contents

12.3.1 TNM classification of prostate tumours

12.3.1.1 Prostate

(ICD-0 C61)

12.3.1.2 Rules for classification

The classification applies only to adenocarcinomas. Transitional cell carcinoma of the prostate is classified as a urethral tumour (see UICC TNM Classification of Malignant Tumours, sixth edition1, page 203). There should be a histological confirmation of the disease.

The following are the procedures for assessing T, N and M categories:

- *T categories* Physical examination, imaging, endoscopy, biopsy and biochemical tests
- *N categories* Physical examination and imaging
- *M categories* Physical examination, imaging, skeletal studies, and biochemical tests

12.3.1.3 Regional lymph nodes

The regional lymph nodes are the nodes of the true pelvis, which are essentially the pelvic nodes below the bifurcation of the common iliac arteries. Laterality does not affect the N classification.

12.3.1.4 TNM clinical classification*

T		Primary tumour
TX	Primary tumour cannot be assessed	
T0	No evidence of primary tumour	
T1	Clinically inapparent tumour not palpable or visible by imaging	
	T1a	Tumour incident histological finding in 5% or less of tissue resected
	T1b	Tumour incident histological finding in more than 5% of tissue retracted
	T1c	Tumour identified by needle biopsy (eg because of elevated PSA)
T2	Tumour confined within prostate#	
	T2a	Tumour involves one half of one lobe or less
	T2b	Tumour involves more than half of one lobe, but not both lobes
	T2c	Tumour involves both lobes
T3	Tumour extends through the prostatic capsule^	
	T3a	Extracapsular extension (unilateral or bilateral)
	T3b	Tumour invades seminal vesicles(s)
T4	Tumour is fixed or invades adjacent structures other than seminal vesicles: bladder neck, external sphincter, rectum, levator muscles, or pelvic wall	

Notes:

Tumour found in one or both lobes by needle boipsy, but not palpable or visible by imaging, is classified as T1c.

^ Invasion into the prostatic apex or into (but not beyond) the prostatic capsule is not classified as T3, but as T2.

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N		Regional lymph nodes
	NX	Regional lymph nodes cannot be assessed
	N0	No regional lymph nodes metastasis
	N1	Regional lymph node metastasis

Notes:

Metastasis no larger than 0.2cm can be designated as pN1mi. (see Introduction, pN, page 10.)[1]

M	Distant metastasis	
	MX	Distant metastasis cannot be assessed
	M0	No distant metastasis
	M1	distant metastasis
	M1a	Non-regional lymph nodes(s)
	M1b	Bone(s)
	M1c	Other site(s)

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12.3.1.5 pTNM Patholgoical classification

The pT, pN, and pM categories correspond to the T, N, and M categories.

However, there is no pT1 category because there is insufficient tissue to assess the highest pT category.

12.3.1.6 g Histopatholgoical grading

GX	Grade cannot be assessed
G1	Well differentiated (slight anaplasia) (Gleason 2-4)
G2	Moderately differentiated (moderate anaplasia) (Gleason 5-6)
G3-4	Poorly differentiated/undifferentiated (marked anaplasia) (Gleason 7-10)

12.3.1.7 Stage grouping

Stage I	T1a	N0	M0	G1
Stage II	T1a	N0	M0	G2,3-4
	T1b, c	N0	M0	Any G
	T1, T2	N0	M0	Any G
Stage III	T3	N0	M0	Any G

Stage IV	T4	N0	M09	Any G
	Any T	N1	M0	Any G
	Any T	Any N	M1	Any G

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12.3.1.8 Summary

Prostate	
T1	**Not Palpable**
T1a	<5%
T1b	>5%
T1c	Needle biopsy
T2	**Confined within prostate**
T2a	<half one lobe
T2b	>half one lobe
T2c	both lobes
T3	**Through prostatic capsule**
T3a	extracapsular
T3b	seminal vesicle(s)
T4	**Fixed or invades adjacent structures: bladder neck, external sphincter, rectum, levator, muscles, pelvic wall**
N1	**Regional lymph node(s)**
M1a	**Non-regional lymph node(s)**
M1b	**Bone(s)**
M1c	**Other site(s)**

*Since these guidelines have been developed the UICC have published the seventh edition of TNM Classification of Malignant Tumours.[2] There is no material difference in the definition of the T-, N-, and M-categories, however, there are some differences in stage grouping and risk grouping. See the table below:

Definitions of T-, N- and M- categories

T1	**Not palpable or visible**
T1a	<5% or less
T1b	>5%

T1c	Detected by needle biopsy
T2	**Confined within prostate**
T2a	<half of one lobe
T2b	>half of one lobe
T2c	Both lobes
T3	**Through prostate capsule**
T3a	Extracapsular
T3b	Seminal vesicle(s)
T4	**Fixed or invades adjacent structures**
	No changes from 6th

STAGE GROUPING (ANATOMIC)(UICC)

Stage I	**T1, T2a**	N0	
Stage II	**T2b-2c**	No	
Stage III	T3	N0	
Stage IV	T4	N0	
	Any T	N1	
	Any T	Any N	M1
			Change from 6th
			Grade was in 6th

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12.3.2 References

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12.4 Further references

Further references

Further references have been brought to the attention of the Working Party that do not fall within the criteria of reference selection.

These may prove of interest to readers of these Guidelines:

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12.5 Organisations which provide information and/or support for men with advanced prostate cancer

12.5.1 Organisations which provide information and/or support for men with advanced prostate cancer

Cancer Councils in each state: contact Cancer Council Helpline: 13 11 20

Contact Cancer Council Helpline to find your local familial cancer service: 13 11 20

Multicultural Cancer Information Services 13 11 20

Prostate Cancer Foundation of Australia: 1800 22 00 99 website: www.prostate.org.au

Prostate Cancer Support Groups: 1800 22 00 99 website: www.pcfa.org.au

Andrology Australia: Andrology Australia: 1300 303 878 website: www.andrologyaustralia.org

Beyondblue beyondblue: 1300 22 4636 website: www.beyondblue.org.au

Lions Australian Prostate Cancer website: www.prostatehealth.org.au

Carers Australia: 1800 242 636 website: www.carersaustralia.com.au

12.5.1.1 Palliative Care Organisations

Nationwide contact telephone number is 1800 660 055

Palliative Care Council of NSW T: 0403 699 491 E: info@palliativecarensw.org.au W:www.palliativecarensw.org.au	Palliative Care Council of South Australia T: 08 8291 4137 E: pallcare@pallcare.asn.au W:www.pallcare.asn.au
Palliative Care Queensland T: 07 36330096 E: info@pallcareqld.com W:www.palliativecareqld.org.au	Tasmanian Association for Hospice and Palliative Care T: 03 6234 7577 E: enquiries@palliativecareqld.org.au E: tahpc@associationoffices.com.au
Palliative Care Victoria	Palliative Care ACT

T: 03 9662 9644 E: info@pallcarevic.asn.au W:www.pallcarevic.asn.au	T: 02 6273 9606 E: actpc@bigpond.com
Palliative Care WA T: 08 9212 4330 E: pcwainc@palliativecarewa.asn.au W:www.palliativecarewa.asn.au	Palliative Care NT T: 08 8922 8824 E: moq13026@hcinternet.com.au

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12.6 Conflict of interest summary

Conflict of interest summary

Professor Villis Marshall AC -- Chair
Urologist in Clinical Practice
Clinical Director of Surgical and Specialties Service, Royal Adelaide Hospital
Significant input into Guideline development and translating these to community friendly document
Abbott Advisory Board on LUCRIN.

Mr Don Baumber
Consumer
Currently undergoing treatment in Holland

Associate Professor Damien Bolton FRACS
Urologist. Associate Professor, Austin Hospital, Heidelberg
Sponsored to attend a conference by Ipsen Pharmaceuticals and also by Abbott Australasia

Dr Mary Brooksbank AM MB, BS; FRACS; FAChPM'
Director of Palliative Care, Royal Adelaide Hospital and Medical Director, Mary Potter Hospice, Calvary Healthcare, North Adelaide
Senior Lecturer, Discipline of Medicine, University of Adelaide
No conflict of interest to declare in relation to these Guidelines

Professor Suzanne Chambers
Director of Research and General Manager Services
Cancer Council Queensland
No conflict of interest to declare

Ms Helen Crowe
Urology Nurse Practitioner/Urology Research Nurse
Royal Melbourne Hospital
No conflict of interest to declare

Professor RA 'Frank' Gardiner AM
University of Queensland Centre for Clinical Research
Consultant Urologist, Royal Brisbane and Women's Hospital
Member of the Denosumab Advisory Board for Amgen in 2007, member of the Satrplatin Advisory Board for Pharmion in 2006, member of Pfizer's International Steering Committee for Darafenacin (2000–2002), member of Natbio's Medical and Biological Advisory Committee (2003–2007), member of Advisory Board for Roche Products regarding Fleroxacin (QuinodisTN) in 1992.

Not presently a member of any industry boards and none of the above relate to androgen deprivation therapies. (Satraplatin is a cytotoxic drug and Denosumab is a human monoclonal antibody to Rank ligand to prevent bone metastases in prostate and other cancers. Darafenacin is an anticholinergic drug used for treatment of urinary incontinence and Fleroxacin is/was an antibiotic.

Member of a group undertaking commissioned clinical trials for industry for which payment is received and used to bolster finances for research activities. About to commence a trial with abiraterone (which blocks androgen production from the adrenal) in patients with castrate-resistance prostate cancer and a study using an infrared light to destroy BPH tissue in patients primed with a porphyrin to enhance the activity of the infrared light. Hoping to undertake a further study with Amgen imminently with Denosumab in patients with castrate resistant prostate cancer. Presently doing a study with Botox for urinary incontinence and hope to participate in an extension study.

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No conflict of interest to declare

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No conflict of interest to declare

Ms Jill Margo AM
Medical Journalist
Columnist “Men’s Health”
Australian Financial Review
No conflict of interest to declare

Professor Diane O’Connell
Cancer Epidemiology Research Unit

Cancer Research Unit, Cancer Council NSW
Andrology Australia and Prostate Cancer Foundation of Australia provided funding to the Cancer Council NSW to conduct the systematic reviews. However neither organisation had any input into the methods used or the reporting of the information. Subsequently received a grant from PCFA to examine the use of complementary and alternative therapies by men with prostate cancer which arose from the systematic reviews completed for the guidelines.

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No conflict of interest to declare.

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Urologist
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12.7 Abbreviations

Abbreviations

ADT	Androgen deprivation therapy
BMD	Bone mineral density
CAB	Combined androgen blockade
CAM	Complementary and alternative therapies
CI	Confidence interval (see Glossary)
CRPC	Castration-resistant prostate cancer
CT	Computed tomography

DES	Diethylstilbestrol
DEXA	Dual energy x-ray absorptionmetry
EBRT	External beam radiotherapy
EORTC	European Organisation for Research and Treatment of Cancer
GnRH	Gonadotrophin releasing hormone
Gy	A unit of absorbed radiation = to 1rad
HR	Hormone resistant
IGRT	Intensity modulated radiation treatment
IMRT	Image guided radiation treatment
IV	intra-venous
LHRH	Luteinising hormone releasing hormone
M1	Evidence of metastatic disease
M0	No evidence of metastases
MRI	Magnetic resonance imaging
MSCC	Metastatic spinal cord compression
PBS	Pharmaceutical Benefits Scheme – Australian Government
PET	Positron emission tomography
PSA	Prostate specific antigen
QCT	Quantitative computerised tomography
QOL	Quality of life
RANK	Receptor activator of nuclear kappa B
RCT	Randomised controlled trial
RR	Relative risk
RTOG	Radiation Therapy Oncology Group
SES	Socioeconomic status
SRE	Skeletal-related events
SWOG	South Western Oncology Group
TROG	Trans Tasman Radiation Oncology Group
TURP	Trans-urethral resection of the prostate (see Glossary)
XRT	X-ray therapy

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12.8 Glossary

Glossary

Actuarial survival	A method of calculating survival over time.
Adrenal glands	Small glands lying on top of the kidneys which produce a small amount of male hormone.
Anaemia	A lack of red cells in the blood. It can cause tiredness, paleness, weakness and sometimes heart problems
Androgens	Male hormones. The most active male hormone, testosterone, is produced by the testicles. Other male hormones are produced by the adrenal glands.
Androgen deprivation therapy (ADT)	Medical or surgical castration, anti-androgens or oestrogens.
Anti-androgens	Drugs that block the effects of male hormones.
Asymptomatic	Asymptomatic Not having symptoms, symptom-free.
Benign	Not cancerous
Benign prostate enlargement	Non-cancerous enlargement of the prostate. Overgrowth of normal prostate tissue.
Bisphosphonates	A class of drugs that prevent the loss of bone mass.
Bone scan	A test in which a radioactive chemical is injected, then x-rays trace its path throughout the body. The chemical goes to parts of the bone which are abnormal, such as areas of cancer, infection or arthritis. Bone scans can be unreliable and so are often used to give guidance, rather than answers, to a problem.
Benign prostatic hyperplasia (BPH)	A condition causing non-cancerous enlargement of the prostate.
Biopsy of the prostate	Biopsy of the prostate Removal of small pieces of tissue, in this case, from the prostate. Tissue samples are taken from different areas of the prostate, and then examined under the microscope to see if they are cancerous.
Brachytherapy	A type of radiotherapy of the prostate. Involves the insertion of radioactive seeds directly into the prostate which are retained (low-dose brachytherapy). An alternative form (high-dose brachytherapy) involves treatment by temporary insertion of radio-active catheters into the prostate.

Complementary and alternative therapies	Complementary medicine is any intervention that is used in conjunction with standard western health practices. Integrative medicine is an approach that combines standard western health interventions and evidence based complementary medicines. For example: the use of a course of relaxation therapy in conjunction with standard radiotherapy or chemotherapy regime to reduce stress For example: the use of a course of relaxation therapy in conjunction with standard radiotherapy or chemotherapy regime to reduce stress Alternative medicine is an intervention or product offered as an alternative treatment to standard western medical practices.
Castrate-resistant prostate cancer	Progressive disease despite castrate levels of testosterone.
Computed tomography (CT, also CAT Scan)	A series of x-ray pictures are taken in a circle around the body which are processed by a computer.
Combined androgen blockade (CAB)	Anti-androgen and medical or surgical castration.
Complete remission (also, complete response)	This is the term used when, after treatment, there is no sign of any cancer. It is not necessarily the same as ‘cure’, as some cancer cells may be hidden.
Confidence interval (CI)	Quantifies the uncertainty in measurement. When reported as 95% CI, it is the range of values within which we can be 95% sure that the true value for the whole population lies.
Coping strategies	Mental strategies or behaviours used to help a person deal with stressful situations. Coping strategies may be influenced by personality style and the specific situation, and may change over time.
Cystitis	Inflammation of the bladder, often caused by infection.
Cystoscope	A tiny tube with a lighted end which slides along the urethra and is used to examine the bladder.
Depression	A general and long-lasting feeling of being down, often associated with tearfulness, guilt or irritability. Other features include loss of interest or pleasure in activities, lowered energy levels, poor concentration and troubles with sleep and appetite.
Digital rectal examination (DRE)	An examination of the prostate through the wall of the rectum. The doctor inserts a finger in the rectum and feels the shape of the prostate. Irregularities may be caused by cancer.

Dissemination	The act of communicating, distributing or spreading a message or piece of information. The term ‘passive dissemination’ is often used to refer to the distribution, by hand or in mass mailings, of printed education materials, such as clinical practice guidelines.
Dry ejaculation	After a radical prostatectomy, a man may achieve orgasm, but produce no ejaculate. This is because the glands which produce much of the fluid in the ejaculate are removed. See also reverse ejaculation
Effectivenesss	The extent to which a specific intervention, when used under ordinary circumstances, does what it is intended to do.
Ejaculate	Fluid produced at ejaculation, which contains sperm and secretions from glands such as the prostate, seminal vesicles and testicles.
Evaluation	A formal appraisal, using quantitative and/or qualitative data, of the value of a project or program against a standard or set of specified criteria. An evaluation may be done internally or by an independent body. The purpose of the evaluation will determine whether it is designed to assess process, outcome or impact.
Evidence	Data on the effectiveness of a treatment or intervention derived from studies that compare it with an appropriate alternative. Preferably the evidence is derived from a good-quality randomised controlled trial, but it may not be. In areas of medicine that do not involve a therapeutic intervention, such as diagnosis, prognosis, aetiology and screening, evidence constitutes knowledge derived from properly conducted clinical or health services research.
Evidence-based guideline	A statement that is based on scientific literature, explicitly documents the process used to develop the statement, and grades the strength of the evidence used in making clinical recommendations.
Five-year survival rate	A scientific measure used to determine the success of a treatment. It measures the number of people who are alive five years after a particular treatment. It does not mean the patient will only live for five years after having treatment.
General anaesthetic	A drug given to stop a person feeling pain. A general anaesthetic causes temporary loss of consciousness.
Gleason score	A way of grading cancer cells. Low-grade cancers (Gleason score 2, 3, 4) are slower growing than high-grade (Gleason scores 8, 9, 10) cancers.The pathologist identifies the two most common tissue patterns and grades them from 1 (least aggressive) to 5 (most aggressive). The Gleason score is given as two numbers added together to give a score out of ten (for example, 3 + 4 = 7). The first number is the most common pattern seen under the microscope and the second number is the next most common.
Grade	A way of describing how abnormal the cancer cells look, and consequently how aggressive or fast-growing the cancer is likely to be.The most commonly used grading system is the Gleason score, which ranges from 2 to 10 (see above).

Hazard ratio	A measure of how often a particular event happens in one group compared to how often it happens in another group, over time. In cancer research, hazard ratios are often used in clinical trials to measure survival at any particular moment in a group of patients who have been given a specific treatment or a placebo. A hazard ratio of one means that there is no difference in survival between the two groups. A hazard ratio of greater than one or less than one means that survival was better in one of the groups.
Hormone resistance	Prostate cancer cells are dependent on testosterone or male hormone for growth. Withdrawal of male hormone by surgery or by means of drugs is therefore a means of controlling its growth. However, cancer cells may develop which do not need testosterone for growth. The cancer is then said to be 'hormone resistant'.
Hormones	Natural chemical substances that are produced by one body organ, and travel through the bloodstream to other organs where they exert their effects. A well-known example is insulin, which regulates the blood sugar level.
Hot flush	A sudden rush of heat to the face, neck and sometimes chest and back. It can be associated with hormone therapy for prostate cancer.
Hyperthermia	Higher than normal temperature. In the case of prostate cancer, a way of destroying tissue by heating.
Impotence	Inability to achieve an erection firm enough for penetration.
Incidence	The number of new cases of a disease or condition among a certain group of people within a certain period of time.
Incontinence	Inability to hold or control the loss of urine or faeces.
Indolent	Refers to the type of cancer cells which grow only slowly.
Intervention	An action that produces an effect or that is intended to alter the course of a process.
Karnofsky Performance Scale	A scale assigning scores from 0 (non-functioning or dead) to 100 (totally normal function).
Luteinising hormone releasing hormone (LHRH)	This is produced by the hypothalamus in the brain and stimulates the pituitary (another part of the brain) to produce LH (luteinising hormone). This, in turn causes cells in the testicles to produce testosterone, the male hormone.
LHRH agonists	Drugs that interfere with the production of LH (see above) by the pituitary.
Libido	Sexdrive
Local anaesthetic	The technique of making a small part of the body numb so that minor operations can be performed without pain while allowing the patient to remain awake.
Locally recurrent	Cancer that has recurred (come back) after treatment, but which is confined to the prostate or nearby tissues only.

Lymph	A clear, sometimes faintly yellow fluid containing white cells, that is collected from the tissues throughout the body, flows in the lymphatic vessels (through the lymph nodes), and is eventually added to the venous blood circulation.
Lymph glands	Lymph nodes
Lymph nodes	Small, generally pea-sized pieces of tissue found all over the body but easier to feel in the neck, armpits, and groins. Lymph nodes act as filters for foreign substances and commonly become inflamed if there is an infection nearby. They can also harbour cancer cells that have spread from elsewhere.
Malignant	Cancerous
Margin-positive	See Surgical margins
Maximal androgen blockade	Another term for combined androgen blockade (CAB).
Medical oncologist	A specialist in the treatment of cancer who uses chemotherapy
Metastasis	The secondary or distant spread of cancer, away from its primary (initial) site in the body.
Metastatic	Relating to secondary cancer.
Monitoring	The process in which patients are followed up after initial diagnosis and treatment. Monitoring may include clinical examination and/or the regular performance of tests.
Magnetic resonance imaging (MRI)	A way of imaging the inside of the body using magnetic forces and without using x-rays.
Nodules	Small lumps
Oncologist	A specialist in the treatment of cancer.
Orchidectomy (also orchiectomy)	A type of operation which removes the testicles, but usually leaves the scrotal sac or scrotum.
Partial remission (or response)	The situation when, following treatment, signs of the disease process have partially resolved but have not disappeared completely.
Pelvis/pelvic	The area of the body below the waist and surrounded by the hip and pubic bones.
Pituitary	Part of the brain which produces the hormones that stimulate the testicles to produce testosterone (male hormone) and other hormones.
Primary	The site where the cancer began.
Prognosis	The course and likely outcome of a disease, as estimated by a person’s doctor or treatment team.
Prostatectomy	An operation to remove all or part of the prostate
Prostatitis	Inflammation of the prostate. It can be caused by bacteria.

Protocol	A well-defined program for treatment.
Prostate specific antigen(PSA)	A protein produced by the cells in the prostate, which is usually found in the blood in larger amounts when prostate cancer is present. It can be used as a test for prostate cancer or to monitor its recurrence.
Psychosocial	Referring to the emotional, psychological, social and spiritual aspects of human life.
Quality of life (QOL) .	A person's overall appraisal of his or her situation and wellbeing.
Radiation oncologist	A specialist in the treatment of cancer using x-ray techniques.
Radical prostatectomy	An operation which removes the prostate and the seminal vesicles. This is usually done through a cut in the lower abdomen.
Radiotherapy	The use of radiation as x-rays or electrons to kill tumour cells.
Rectum	The last part of the bowel, leading to the anus, and through which stools pass.
Recurrence	The re-occurrence of cancer some time after it was first treated.
Reliability (of a test)	The ability to measure something in a reproducible and consistent fashion.
Response	A change in the size or extent of disease due to treatment.
Retrograde ejaculation	Also called reverse ejaculation. This may occur after surgery for benign conditions of the prostate. The ejaculate travels back into the bladder instead of exiting out through the penis. This means a man is usually infertile (cannot produce offspring in the conventional way), but he can still achieve orgasm.
Scrotum	A pouch of skin which contains the testicles and some other parts of the male reproductive system. It hangs outside the body and below the penis.
Seminal vesicles	Glands that lie very close to the prostate and produce secretions which form part of the ejaculate.
Staging	The process of determining the extent of the disease. A system for describing how far the cancer has spread. The most common is the TNM system described in Appendix 3. A second and older system sometimes referred to, is the Jewett system: *Stage A*—Prostate cancer that began and is found in the prostate only. Divided into two stages. *Stage B*—Prostate cancer began in the prostate and is more advanced than Stage A. *Stage C*—Prostate cancer that began in the prostate, has grown beyond the outer layer of the prostate to nearby tissues, and may be found in seminal vesicles (glands that help produce semen). Stage D—Prostate cancer that began in the prostate and has spread lymph nodes or far from the prostate, or to other parts of the body, often to the bones.

	Each stage is divided into subgroups, which may be viewed at <www.cancer.gov/templates/db-alpha.aspx?expand=S> accessed 8 July 2009.
Stricture	Scar tissue which obstructs fluid flow. In the case of a urethral stricture, urine flow is obstructed.
Support	People on whom the patient can rely for emotional caring, and reinforcement of a sense of personal worth and value. Other components of support may include practical help, guidance, feedback and someone to talk to.
Surgical margins	After a radical prostatectomy, the edges of the tissue which has been removed are examined to see if cancer cells are present. If they are not (negative surgical margins) the chance is higher that all of the cancer has been removed.
Survival — disease free	The proportion of people surviving to a given time, such as five years, without evidence of disease.
Survival — prostate cancer specific	The proportion of people who do not die of prostate cancer in a given period, such as five years.
Systemic	Relating to the whole body.
Systematic review	A review of a clearly formulated question that uses systematic and explicit methods to identify, select and critically appraise the relevant literature, and to collect and analyse data from the studies that are included in the review. Statistical methods (meta-analysis) may or may not be used to analyse and summarise the results of the included studies.
Testicles	Glands which produce sperm and the male hormone, testosterone. They are found in the scrotum.
Testosterone	The major male hormone. It is produced by the testicles.
Trans-rectal ultrasound (TRUS)	A means of imaging the prostate in order to locate cancer. The ultrasound probe is placed in the rectum
Tumour	Any swelling. In the context of cancer, the word usually refers to malignant (cancerous) lumps.
Trans-urethral resection of the prostate (TURP)	This is a common operation for benign enlargement of the prostate, but only occasionally used to treat prostate cancer. An instrument is inserted, under anaesthetic, along the urethra (urine tube) and removes prostate tissue which may be blocking the flow of urine.
Urethra	The tube which carries urine and ejaculate along the length of the penis and to the outside.

This glossary is adapted from the Clinical Practice Guidelines: evidence-based information and recommendations for the management of localised prostate cancer. A report of the Australian Cancer Network Working Party on management of localised prostate cancer. October 2002, NHMRC, Canberra.

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