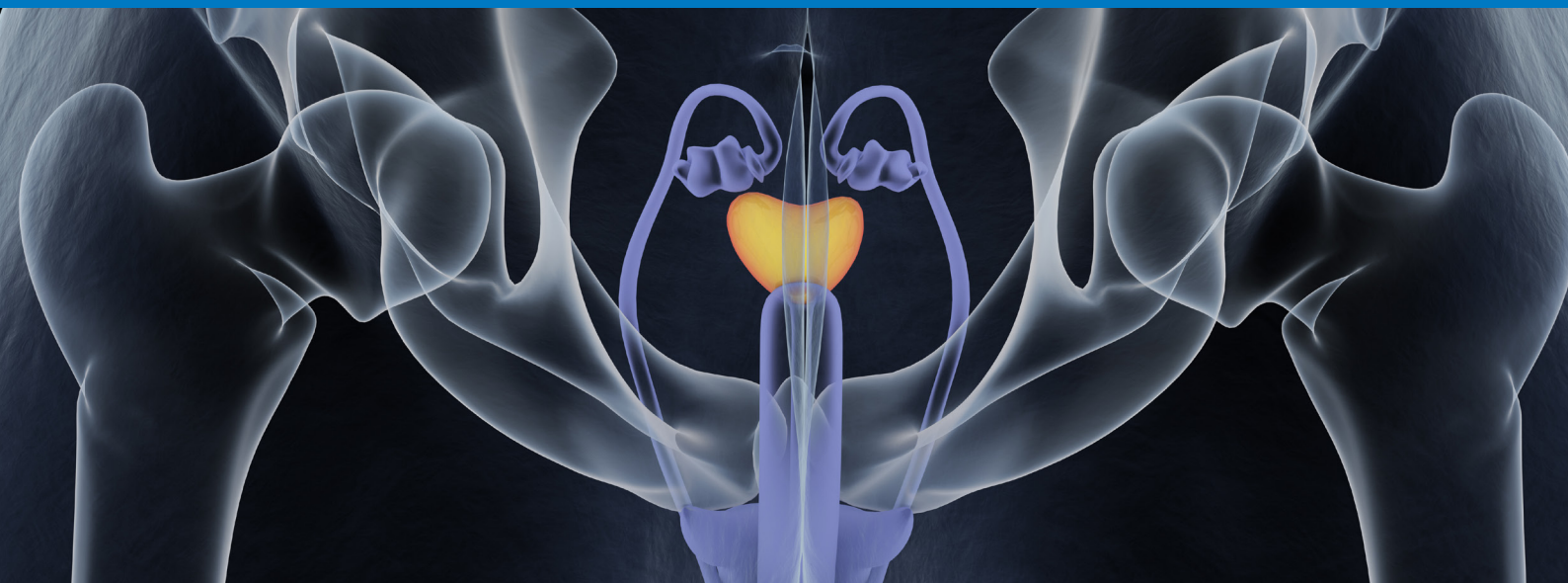


Modern Radiation Therapy and Hormone Therapy for Localised Prostate Cancer

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awareness of the benefits of radiation therapy in cancer care.

This article discusses the importance of referral of patients with prostate cancer for consideration of radiation therapy if active treatment is considered.

Introduction

Prostate cancer affects one in five men and accounts for over three thousand deaths in Australia each year.¹ It is the second most commonly diagnosed cancer in Australian males (following non-melanoma skin cancer) and is the second most common cause of cancer death (after lung cancer).²

Although there is no formal screening program for prostate cancer in Australia, many men have prostate-specific antigen (PSA) testing and this is the most common path leading to a diagnosis of prostate cancer. Most men these days present with disease that is confined to the prostate or the immediate extra-prostatic fat (localised prostate cancer) and have no clinical evidence of nodal or distant metastases. The majority of men present with no associated urinary symptoms, although obstructive urinary symptoms should be investigated as they may be associated with prostate cancer. Urological symptoms

Take Home Messages

- ✓ GPs can help to ensure men know all their treatment options for prostatic cancer.
- ✓ Treatment for prostate cancer is rarely urgent.
- ✓ Modern radiation therapy is as effective as prostatectomy in curing prostate cancer.
- ✓ Advances in radiation therapy have significantly reduced serious side-effects and have improved the patient experience.
- ✓ Hormone therapy or androgen deprivation therapy is often used with radiotherapy in the curative setting.
- ✓ GPs have a key role in managing the potential morbidity of androgen deprivation therapy.

are, however, usually associated with benign prostatic hypertrophy. Less commonly, symptoms such as haematuria, haematochezia (fresh blood per rectum), bowel changes, and/or renal impairment from bladder outlet obstruction signify locally advanced disease.

What are the Treatment Options for Localised Prostate Cancer?

There are nearly always several options for the treatment of localised prostate cancer. There is virtually never a need for immediate treatment, in particular, urgent prostate removal. In the vast majority of cases men have at least several weeks, if not longer, to see all relevant specialists (including both a surgeon and radiation oncologist), and to consult with their General Practitioner (GP) and loved ones prior to making a decision about which treatment is best for them as an individual. This model places the man *at the centre* of decision-making and is the ideal management of localised prostate cancer, as demonstrated Figure 1. It is important to discuss this model with men who are being referred to a urologist for further evaluation where a potential diagnosis of prostate cancer is being entertained, even if the diagnosis has not yet been confirmed.

Men can be told by their GP that IF their biopsies show prostate cancer, it is important that they take time to consider all their treatment options. Understandably, this is a frightening situation. However, this will ensure that men are adequately informed about the pros and cons of management options and that they can choose the treatment that is right for them. There is good evidence that this reduces the risk of regret about their decision in the long-term.³ We strongly encourage men with intermediate-risk and high-risk prostate cancer (see below) to consult radiation oncologists about the non-surgical options for treatment. This position is supported by Cancer Council Australia and the Prostate Cancer Foundation of Australia (PCFA). GPs are encouraged to ensure there is a referral to a radiation oncologist as part of the decision-making and to let the urologist know if this has not been already done.

There is no good evidence that prostatactomy followed by radiation therapy has any advantage over radiation therapy alone for high-risk or advanced cases.

Treatment options include radical prostatectomy (open or robot-assisted), radiation therapy (external beam or brachytherapy) or in low-risk cases, active surveillance. Table 1 shows the options

according to prostate cancer risk groupings; these are based on the PSA at presentation, tumour stage (clinical PR findings) and Gleason score (tumour grading).

There is good evidence that the chance of cure with modern radiation therapy is equal to that of radical prostatectomy for prostate cancer in all risk groups.¹⁻⁴ Most men considering some form of active treatment are in the intermediate and high-risk category and many randomised and prospective studies show equivalence of cancer cure or control for surgical and non-surgical options.⁴⁻⁷ Radiation therapy used after prostatectomy (known as adjuvant or salvage radiation therapy) may be required post-operatively in at least 40% of cases and often provides long term cancer control or cure.⁸ This is to eradicate cancer that was not able to be completely removed with surgery. This situation occurs when cancer cells are either known to be left behind or are found to be left behind when the PSA rises in the future.

However, it is important to note there is no good evidence that prostatectomy followed by radiation therapy as a planned approach to treatment gives better long-term outcomes when compared with radiation therapy (and ADT) alone, even for more aggressive cancers. However the risk of toxicity and complications are greater when prostatectomy and surgery are added. Therefore, if there is a high likelihood that post-prostatectomy radiation therapy will be required for positive margins it may be preferable that a non-surgical approach is taken.

Modern Radiation Therapy for Prostate Cancer

In Australia, external beam radiation therapy (EBRT), also called "radiotherapy", is the standard form of radiation available at all radiation therapy centres. Brachytherapy is available at limited sites (more can be read about brachytherapy at www.targetingcancer.com "Brachytherapy for Prostate Cancer" Section). This discussion will be limited to EBRT from now on.

Radiation therapy for localised prostate cancer has changed dramatically over the last two decades, resulting in improvements in both disease control and treatment-related toxicity. Radiation therapy is delivered by a linear accelerator (also called a "Linac"), that generates megavoltage photon beams that can be orientated and shaped to match the unique tumour position, size and dimensions of an individual patient. Image-guided intensity modulated radiation therapy (IMRT) is now the standard of care across Australia, creating highly conformal treatments that maximise the dose delivered to the target whilst sparing normal tissues, such as the bladder and bowel.

The prostate is imaged prior to each treatment using dedicated cone beam computed tomography (CBCT), or plain x-rays, taken on the machine. Often these images are also matched using small gold "fiducial" markers permanently inserted into the prostate under transrectal or ultrasound guidance as part of the planning process.

Shifts of the patient or treatment couch can be made, if needed, to ensure millimetre accuracy. Figure 2 demonstrates a radiation therapy treatment plan in which the high radiation dose has been 'sculpted' around the front of the rectum to reduce the chance of side-effects.

For more about the recent advances in radiation therapy for prostate cancer, go the GP portal at www.targetingcancer.com.au/about-radiation-oncology/for-health-professionals, click on the heading "Useful Resources" and scroll down to find the review article recently published by Gorayski et al: "Advances in Radiotherapy Technology for Prostate Cancer: What Every GP should know".⁸

What are the Practicalities for Men Undergoing Radiation Therapy for Localised Prostate Cancer?

Radiation therapy for localised prostate cancer is delivered as an outpatient service, once daily on a weekday, over several weeks. The standard course consists of thirty-nine or forty short treatments over this period.⁹ More recently, several studies have shown the safety and effectiveness of reducing the overall treatment time to four weeks, giving only twenty treatments.¹⁰ In many centres, this shorter course is becoming commonplace for many men with prostate cancer. Each treatment session, also called a "fraction", takes approximately five to ten minutes, depending on the patient's body habitus and the radiation therapy technique. The patient is monitored and supported throughout the treatment by a team, including radiation oncologist, specialist nurses and radiation therapists.

Patients will be given advice about trying to achieve a regular bowel habit through dietary modification and/or medication during the planning and treatment period, in order to manage potential movement of the prostate during radiation therapy. Before each fraction is delivered, patients repeat the same routine, such as holding a comfortably full bladder and maintaining an empty rectum.

The majority of men experience mild side-effects during treatment and just afterwards. These include some fatigue, and often local symptoms due to irritation of the urethra, bladder base and rectum. Less than 8% experience significant late urinary or bowel symptoms, and if these do occur, they can usually be treated and/or are not permanent.¹¹ Of note, urinary incontinence is very uncommon with radiation therapy.¹¹ The treatment sessions are painless and the vast majority of men are able to continue with normal activities of daily living (including employment) throughout their course of radiation therapy.

At the time of publication, over 60% of patients in Australia undergo radiation therapy for prostate cancer in the public sector, hence for the majority of patients there is no (or very minimal) financial cost.¹² For more on the practicalities and side-effects of radiation therapy go to: www.targetingcancer.com.au/treatment-by-cancer-type/prostate-cancer.

What is the Role of Hormone Therapy for Localised Prostate Cancer?

Hormone therapy used for prostate cancer is also known as 'androgen deprivation therapy' (ADT) and may be given to men before, during and/or after curative radiation therapy, depending on their individual risk profile. Androgen deprivation therapy is also used for recurrent or metastatic prostate cancer, though in these cases it is usually prescribed indefinitely or intermittently over the remainder of the man's life.

ADT also reduces PSA levels independently of radiation therapy and therefore may confound PSA interpretation for several months, or even more than a year, after treatment is completed.

When used with radiation therapy, the purpose of ADT is to reduce the size of the gland and sensitise the prostate cancer to radiation. Luteinizing hormone-releasing hormone (LHRH) agonists are commonly used via a monthly or third monthly depot preparation, however other hormone drugs are sometimes used. The duration of ADT in this setting ranges from six to twenty-four months and has been shown in scientific studies to increase the treatment cure rates for intermediate and high-risk prostate cancers.¹³

The side-effects of hormone therapy may include reduced libido, erectile dysfunction, hot flushes, osteopenia and osteoporosis, loss of muscle mass, central weight gain, mood swings, insulin resistance, decline in cognitive function, fatigue and gynaecomastia. However, shorter courses (e.g. six months), are generally well tolerated and men are very variable in the degree to which they are affected by hormone-related symptoms. Table 3 summarises the key management points to guide GPs in managing the toxicity of ADT.

ADT also reduces PSA levels independently of radiation therapy and therefore may confound PSA interpretation for several months, or even more than a year, after treatment is completed. Once the hormone therapy is ceased, side-effects usually disappear over time as serum testosterone levels recover. However in some older men with longer courses of androgen deprivation therapy, the testosterone does not always return to normal.

Hot flushes can be annoying for men on ADT. Usually if they are reassured that these are normal and will resolve as their testosterone

recovers, they do not need any special therapy for these. Other hormone medications, such as cyproterone acetate, may alleviate these. However, usually the flushes are at their peak just after the luteinising hormone-releasing hormone is commenced and then they decline in severity. They may get worse again for a brief time as the testosterone returns. The issue with medical treatments for flushes is that they are not effective in all cases and may take weeks to months to act, by which time the ADT may have been completed, or the flushes improved of their own accord. Rarely men may need to discuss other treatment for flushes with their oncologist or an endocrinologist; a planned course of ADT is occasionally shortened due to intolerance. Regular exercise and keeping cool at night (for instance with a fan and light bedding) may be useful in reducing flush severity.

GPs have a key role in managing the side-effects of hormonal therapy including providing advice about the importance of regular weight-bearing exercise, diet and bone health, monitoring patients for metabolic syndrome and optimising medications for pre-existing comorbid conditions. Of particular importance is the value of weight-bearing exercise, which has been shown in several randomised trials to enhance health- and disease-specific quality of life in men with prostate cancer undergoing ADT.¹⁴

Radiation oncologists often refer patients to services provided by physiotherapists and exercise physiologists who have a special interest in keep men with prostate cancer as fit and well as possible through and beyond treatment.

Table 1: Management Options for Localised Prostate Cancer According to Risk Group (*Intellectual property of the authors*)

	Low risk	Intermediate risk	High risk
PSA	0 to 10 ng/ml and	10 to 20 ng/ml and	>20 ng/ml or
T-stage	T1 – T2a and	T1 – T2b and	T2c – T4 or
Gleason score	6 or lower	7	8 or higher
Management options	<ol style="list-style-type: none"> 1. Active surveillance 2. Radical prostatectomy 3. EBRT 4. LDR brachy 	<ol style="list-style-type: none"> 1. Radical prostatectomy 2. External beam RT +/- ADT 3. LDR brachy 	<ol style="list-style-type: none"> 1. External Beam RT + ADT 2. Radical prostatectomy (+ adjuvant EBRT if margins involved) 3. EBRT/HDR brachy + ADT

Low, intermediate and high risk groups are defined according to D’Amico classification.¹⁵

PSA= prostate specific antigen;

RP= radical prostatectomy;

EBRT= external beam radiation therapy;

ADT= androgen deprivation therapy;

LDR= low dose rate;

HDR= high dose rate.

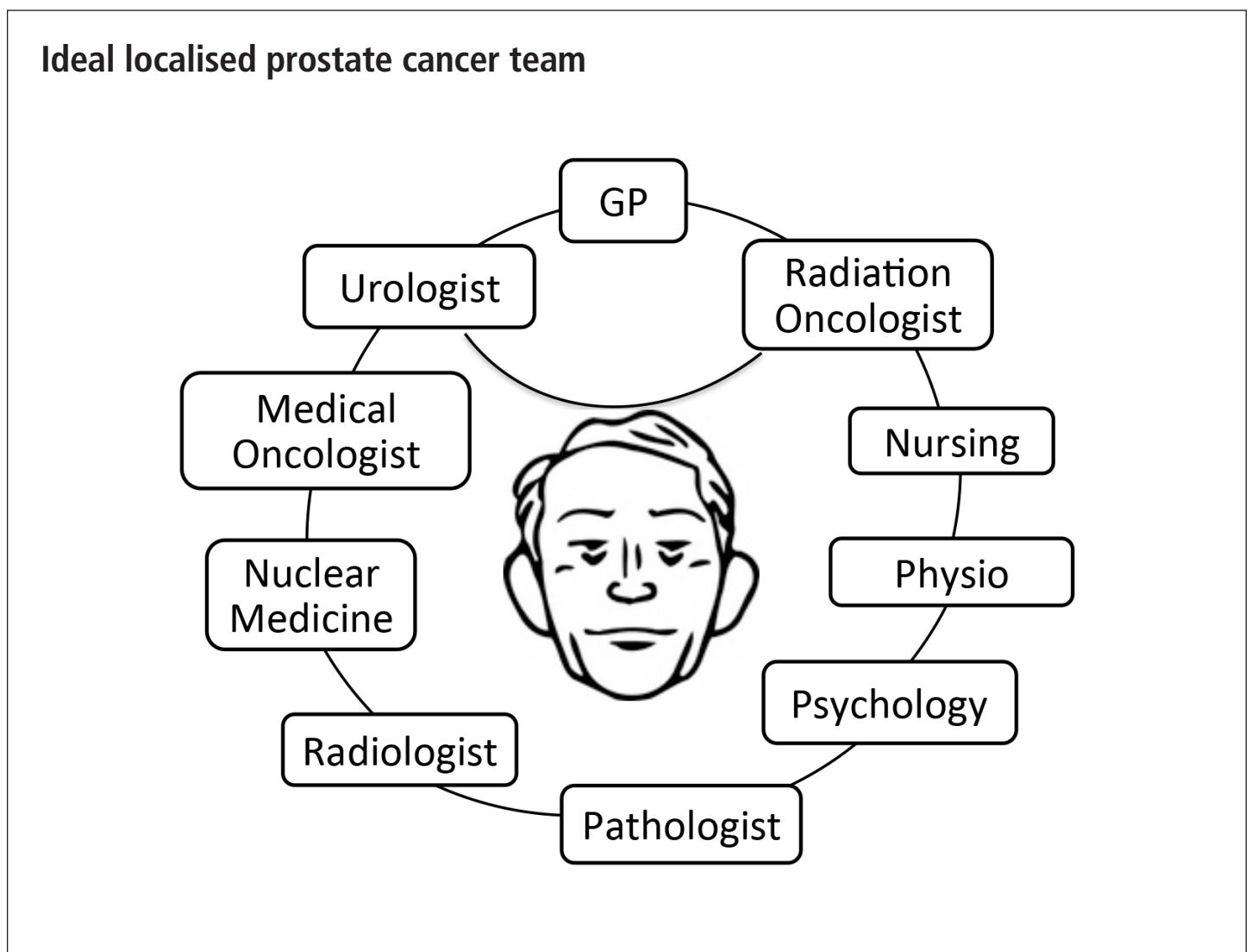
Table 2: Comparisons between radical prostatectomy and radiation therapy (*Intellectual property of the authors*)

Radical prostatectomy (open or robot-assisted)	External beam radiation therapy (EBRT)
<ul style="list-style-type: none"> ✔ In-patient stay usually less than seven days, followed by recovery at home four to six weeks ✔ Must be fit for surgery <p>Potential complications:</p> <ul style="list-style-type: none"> ✔ Anaesthetic and peri-operative risk ✔ Urinary incontinence ✔ Vesico-ureteric stricture ✔ Early erectile dysfunction ✔ Rectal injury (rare) <p>Adjuvant EBRT may be indicated for high risk pathological features (e.g. positive margins)</p>	<ul style="list-style-type: none"> ✔ Out-patient treatment over several weeks, ten to fifteen minutes each day, not on weekends ✔ Must be able to lie flat for twenty minutes <p>Potential complications (see details of early versus late):</p> <ul style="list-style-type: none"> ✔ Urinary symptoms ✔ Bowel symptoms ✔ Later erectile dysfunction ✔ Second malignancy (very rare)

Table 3: Key Management Points to Guide GPs in Managing the Toxicity of Androgen Deprivation Therapy

Duration of Androgen Deprivation Therapy	Key Management Points
Short-course Androgen Deprivation therapy (less than six months) For intermediate risk cancers	<ul style="list-style-type: none"> ✔ Regular exercise ✔ Prevention of weight gain
Longer-course Androgen Deprivation Therapy (more than six months) For high risk cancers	<ul style="list-style-type: none"> ✔ Monitor cardiac risk factors ✔ Cardiology review ✔ Bloods: serum glucose, lipids ✔ Bone health: annual DEXA scan, consider bisphosphonates and endocrinologist review ✔ Resistance exercise ✔ Counsel regarding weight and diet

Figure 1: The gold standard management model for localised prostate cancer *(Intellectual property of the authors)*



Video Resources

	Low risk	Intermediate risk	High risk
PSA	0 to 10 ng/ml	10 to 20 ng/ml	>20 ng/ml
T-stage	T1 – T2a	T1-T2b	T2c – T4
Gleason	6 or lower	Gleason 7	8 or higher
Management options	<ul style="list-style-type: none"> Active surveillance Radical prostatectomy External beam RT LDR brachytherapy 	<ul style="list-style-type: none"> Radical prostatectomy External beam RT +/- ADT LDR brachytherapy (selected cases) 	<ul style="list-style-type: none"> External Beam RT + ADT Radical prostatectomy + adjuvant EBRT EBRT/HDR brachytherapy + ADT

An Update for GPs on Modern Radiation Therapy & Hormones for Prostate Cancer with A/Prof Sandra Turner

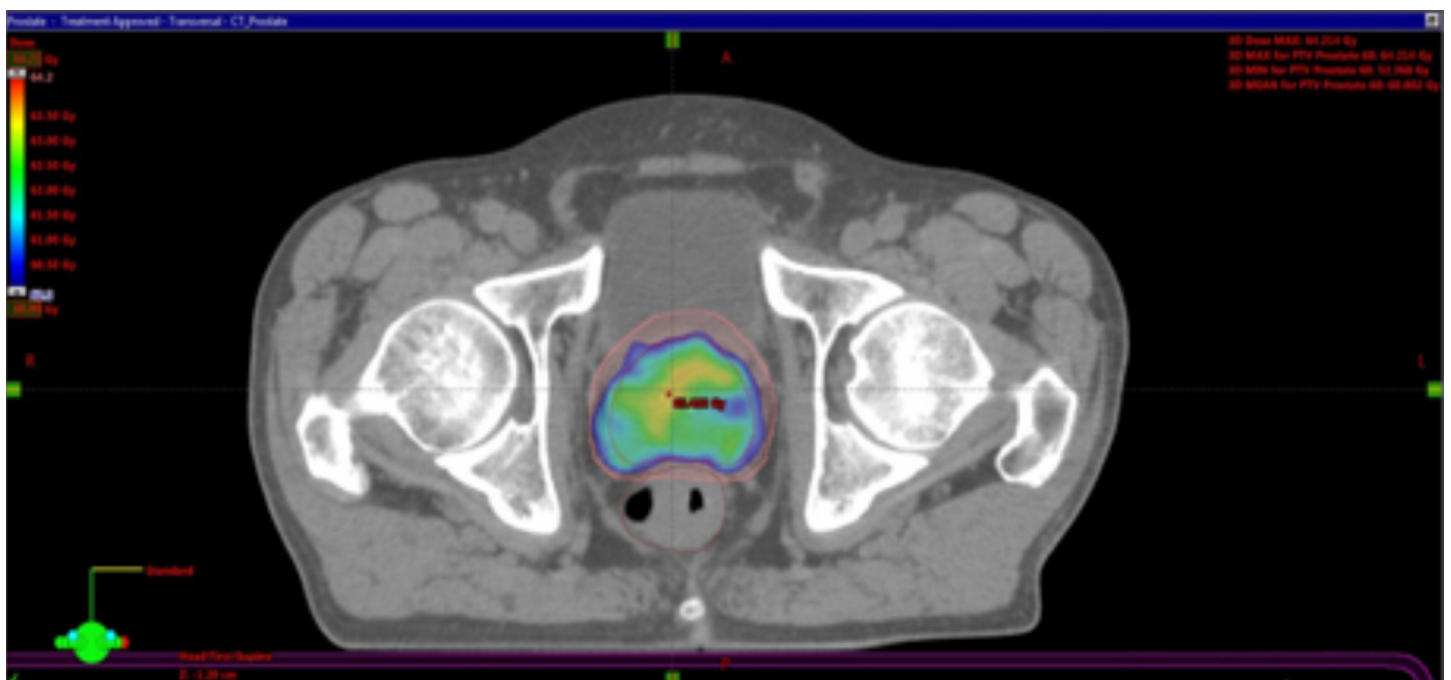
Radiation Therapy with A/Prof Jeremy Millar

Brachytherapy with A/Prof Jeremy Millar

Exercise as Medicine for Prevention and Management of Cancer with Prof Rob Newton

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Figure 2: Radiation therapy plan using IMRT for localised prostate cancer, showing how the high radiation dose can be bent around the front of the rectum to reduce the risk of side-effects (with gratitude to the patient for granting consent for use)



Further Reading

Gorayski P, Pinkham MB, Lehman M. *Advances in radiotherapy technology for prostate cancer: What every GP should know*. Australian Family Physician. 2015; 44: 663-67.

Declaration

A/Prof Sandra Turner and Dr Lucinda Morris were commissioned by Healthed for this article. The ideas, opinions and information presented are solely those of the authors. The advertiser does not necessarily endorse or support the views expressed in this article.

The authors declare no significant competing financial, professional or personal interests that might influence this article.

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