

Prostate cancer

Part 2. options in treatment

Prostate cancer is a common malignancy in Australian men, and the choice of treatment for each individual will depend on many factors. All options must be discussed fully with the patient prior to making any therapeutic decisions.

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Treatments for localised cancer

The management options for localised, potentially curable prostate cancer are:

- radical prostatectomy
- external beam radiotherapy
- low dose rate brachytherapy (seed therapy)
- combination radiotherapy – that is, high dose rate brachytherapy and external beam radiotherapy)
- watchful waiting.

Factors that need to be taken into consideration when selecting treatment include:

- characteristics of the cancer (including the clinical stage, Gleason score, PSA level and histological characteristics)
- the size of the prostate and presence of urinary symptoms
- the patient's age, comorbidities and life expectancy

- general body characteristics (such as obesity, previous radiotherapy or injury).

Each patient's concerns and priorities need to be assessed, with regard to cure as well as to potential side effects. It is mandatory that a full discussion of all options be undertaken prior to making a therapeutic decision because each form of therapy has its own indications, cure rate and complications. Second opinions (clinical and pathological) are being encouraged.

Complications arising from different therapies for localised prostate cancer are listed in Table 1. Treatments for impotence, rectal problems and incontinence resulting from surgery or radiotherapy are discussed in the box on page 2.

Radical prostatectomy

The ideal patient for radical prostatectomy is a man who accepts the risks of surgery, is aware of all his

IN SUMMARY

- Long term ongoing support is mandatory for the patient with prostate cancer, not only to monitor the progress of the disease but also to help manage side effects. Cancer support groups make a large contribution to patient care.
- Traditional radiotherapy has lacked accuracy and resulted in damage to adjacent organs. Side effects have been reduced and results improved by brachytherapy (with or without external radiotherapy), conformal radiotherapy and adjuvant hormone therapy. Addition of hormone therapy to radiotherapy has also improved long term outcomes.
- Combination of brachytherapy with external beam radiotherapy allows successful therapy for more advanced cancers that are often not amenable to surgical cure.
- Hormone therapy is the mainstay of treatment for advanced prostate cancer. Hormones may be given intermittently or continuously. Intermittent use is not as proven as continuous use, but it may be more suitable for patients who are likely to be taking hormone therapy for many years.

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options, and has a clinically localised cancer with at least 10 years of life expectancy. Patients are usually in hospital for three to six days, and have a catheter for three to nine days (including hospitalised days).

For localised cancer, the cure rates for radical prostatectomy (10-year, PSA-progression-free survival) are 85% for organ-confined disease and 82% for specimen-confined disease. In a series of over 1000 cases, the overall 10-year actuarial disease-free survival was approximately 60%. These results can be improved further if adjuvant radiotherapy is used in patients who have extracapsular disease or a positive surgical margin. If a PSA recurrence occurs some time after surgery, the time to death from prostate cancer still averages 13 years and may therefore not impact on the life expectancy of an older man. Even patients with poorly differentiated tumours can be cured surgically if the disease is detected while confined to the organ.

Side effects of treatment (including incontinence and impotence) have become less common with improved surgical techniques and patient selection. In an Australian surgical series at St Vincent's Hospital in Sydney of 732 patients, there was a zero mortality; the major complication rate in the last 200 cases was less than 3%, with a 1% incidence of severe incontinence.

Although impotence remains a common problem of surgery, an erectile nerve-sparing procedure can preserve potency in up to 70% of carefully selected patients, especially those in younger age groups. The technique has improved continuously over the past 10 years, as has the selection of patients to undergo the procedure. At this stage, the use of sural nerve grafts should be regarded as experimental, but promising.

The likelihood of impotence is dependent on many factors, including the preoperative erections, standard of nerve sparing, duration of follow up and the use of early stimulation of erections.

Table 1. Complications of treatments for localised prostate cancer

Complication	Radical prostatectomy	External beam radiotherapy	Low dose rate brachytherapy	Combination radiotherapy*
Mortality	0 to 0.2%	<0.1%	0%	<0.2%
Severe incontinence (requiring regular use of pads)	0.5 to 2%	<1%	<1%	<1%
Severe bowel damage	0%	2 to 3%	<1%	<1%
Stricture	0.6%	4%	0%	4%
Frequency (severe symptoms often lasting more than 6 months)	0%	<10%	30%	<10%
Impotence (assessed 5 years after surgery)	30 to 80% [†]	50%	20 to 40%	50%
Chronic diarrhoea	0%	1 to 2%	0%	<1%

* Comprises high dose rate brachytherapy and external beam radiotherapy.

[†] Dependent on the patient's age and the nerves spared.

Treating complications of surgery and radiotherapy

Impotence

Impotence is common after surgery or radiotherapy. Sildenafil (Viagra), penile injections, vacuum devices and penile implants each have a role. After surgery, sildenafil is successful in only 30 to 40% of patients; after seed therapy, success rates are as high as 80 to 100%. After surgery or radiotherapy, orgasm is still achievable but ejaculation is absent.

Rectal problems

Rectal problems predominantly occur after radiotherapy. Acute proctitis during and after radiotherapy can be treated with corticosteroid enemas (Predsol Retention Enema or Colifoam Rectal Foam). If chronic bleeding occurs, topical formalin or laser therapy given under general anaesthesia has a high success rate.

Incontinence

Incontinence most commonly occurs after radical prostatectomy, although improved techniques have minimised the incidence. Mild incontinence will often improve with pelvic floor exercises over a period of six to 12 months. If persistent incontinence occurs, a series of collagen implants (four treatments often being necessary) or Macroplastique may cure the problem. In cases of severe or ongoing incontinence, an artificial sphincter may be used.

Some patients with partial recovery of erections will respond to sildenafil (Viagra), generally from at least one year after surgery. After a sufficient recovery period, up to 70% of younger men with normal preoperative erections can have a satisfactory return of erections (possibly up to 80% with sildenafil).

External beam radiotherapy

Radical radiation therapy is still an important management option for patients with localised prostate cancer. For low risk cancers, the results are similar to those of surgery; however, the relapse rate appears to be higher if the cancer becomes more extensive or more aggressive.

Traditionally, radiotherapy has been delivered over six or seven weeks. The advantage of radiotherapy is that it can be performed on unfit patients and patients who wish to avoid surgery. The disadvantage is the difficulty of salvage surgery if it fails; on the other hand, radiotherapy may safely follow surgery.

Short term side effects include radiation sickness, proctitis and cystitis, all of which usually resolve within three to six months. In many patients, rectal compliance decreases, leading to frequent bowel actions.

Traditional radiotherapy has lacked accuracy and resulted in damage to adjacent organs, leading to a 3 to 5% incidence of serious damage to the bowel and bladder and a 50% incidence of impotence. Side effects have been reduced and results improved by three new concepts – dose escalation (which provides higher doses of radiotherapy, such as brachytherapy), conformal radiotherapy (which uses modern technology to focus radiotherapy more accurately and minimise damage to adjacent organs), and adjuvant hormone therapy.

Low dose rate brachytherapy

Low dose rate brachytherapy involves the implantation of radioactive pellets or seeds into the prostate (Figure 1). The technique is only suitable for patients who have a low risk cancer and a small prostate, as well as minimal urinary symptoms. The ideal patient is a man over 60 years of age who satisfies these criteria and wishes to minimise the side effects of therapy.

The great advantages of low dose rate brachytherapy are its single-session,

outpatient nature and minimal morbidity. The 10-year, disease-specific survival for low risk cancers is identical to surgery; 12-year data from the USA suggest that this modality can control the disease in 60% of patients. Side effects are minimal, with incontinence and rectal damage being rare. Impotence may occur in 20 to 30% of patients, but it is generally less severe than that occurring after surgery, and responds well to sildenafil.

In the largest series in Australia (almost 100 cases), which was conducted at St Vincent's Hospital in Sydney, side effects have been minimal and results appear to be comparable to international results.

Combination radiotherapy

Combination radiotherapy involves high dose rate brachytherapy given in combination with a much lower dose of external beam radiotherapy. High dose rate brachytherapy requires placement of hollow iridium wires into the prostate under general anaesthesia; radiotherapy is administered through the wires for the next 48 hours (Figure 2). This technique allows a much greater dosage to be applied to the prostate and can be performed very accurately with CT guidance.

The advantages of high dose rate brachytherapy are minimising damage to

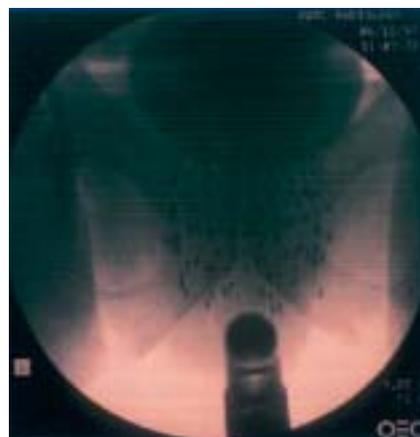


Figure 1. The implanted pellets visible on x-ray.

the adjacent rectum and maximising the dosage (especially for more aggressive tumours) to increase the chance of cure. International data for this treatment combination have resulted in 10-year disease-free survival rates of 80 to 90% – even in men with cancers of intermediate grade.

In more aggressive tumours that may not be amenable to surgery, combination therapy or newer forms of conformal radiotherapy may become the standard of care. Therefore, the ideal patient for high dose brachytherapy is a man who has a more locally advanced high grade cancer that may have extended beyond the capsule and a low chance of surgical cure.



Figure 2. A patient receiving high dose rate brachytherapy administered via iridium rods for locally advanced prostate cancer.

The incidence of rectal damage with high dose rate brachytherapy in combination with external beam radiotherapy has decreased to as low as 1%. The side effect profile in a series at Sydney's St Vincent's Hospital has been excellent.

Watchful waiting

Watchful waiting involves regular digital rectal examinations and PSA estimations, and possible repeat biopsies in patients with known prostate cancer. Over a period of 15 years, patients with well differentiated tumours have a very low chance of dying of their cancer and a much higher chance of dying of other diseases. This is especially true in elderly patients, and watchful waiting has therefore become particularly appropriate for elderly men who have small, well differentiated tumours and a life expectancy of less than 15 years.

The watchful waiting approach is rarely (if ever) recommended for younger men or for those with more aggressive tumours. In a study of 514 patients, 75% of men diagnosed before the age of 70 years died as a result of their cancer. Some younger patients with well differentiated tumours will, however, defer treatment until there is evidence of progression.

Two disadvantages of watchful waiting are the unpredictable nature of the tumour and the fact that PSA levels do not necessarily reflect its growth. (The latter is particularly true in patients taking hormone medications that may affect PSA readings, making it even more difficult to follow these patients.)

Treatment for advanced cancer

Patients with advanced prostate cancer are generally men who have extensive disease in the pelvis, metastases in the lymph nodes or bone or a PSA level greater than 50 ng/mL, or men in whom local treatment has failed.

Bilateral orchidectomy is the gold standard for testosterone reduction.

However, although it offers immediate relief from metastatic pain and eliminates problems of compliance, orchidectomy is psychologically unacceptable to most men. Hormone therapy is the mainstay of treatment in this group.

When hormone therapy is commenced, the vast majority of patients get excellent initial symptomatic relief, even in the presence of painful metastases. Regular PSA measurements are the best way to monitor response.

Some patients elect to delay hormone therapy in the interest of avoiding side effects. These men may have had a PSA recurrence after failed initial therapy or be older asymptomatic men with metastatic disease. In patients who have less advanced disease, the cancer ultimately becomes refractory to hormone therapy (after three to five years, or even longer). Most patients who develop hormone refractory disease die within 12 months.

Which hormones should be used?

Leuprorelin acetate (Lucrin) and goserelin acetate (Zoladex), which are LHRH analogues, are commonly used for chemical castration. However, these agents cause an initial testosterone flare that should be prevented with concomitant use of an antiandrogen for the first two to four weeks' duration. LHRH analogues are available in monthly, three-monthly and, more recently, four-monthly depot preparations.

The nonsteroidal antiandrogens flutamide (Eulexin, Flutamin, Fugerel), bicalutamide (Cosudex) and nilutamide (Anandron) have similar action. These agents are generally used in association with LHRH analogues, but can be used alone in sexually active men to sometimes prevent impotence. Careful monitoring of liver function tests is essential in patients taking antiandrogens.

Cyproterone acetate (Androcur, Cypro, Procur) is a steroidal antiandrogen that can be used alone or with LHRH analogues. Oestrogens have fallen out of

favour because of their cardiovascular side effects.

Should hormones be commenced immediately or later, or intermittently?

Immediate hormone therapy is appropriate for symptomatic patients; however, its timing in asymptomatic patients remains controversial. There is increasing evidence to suggest that earlier use of hormone therapy improves survival, but this benefit must be balanced against side effects. Most patients choose immediate therapy, although older asymptomatic patients may choose delayed therapy after informed consent. Patients with a PSA recurrence after previous failed surgery or radiotherapy often opt for a period of observation to ascertain the rate of PSA rise prior to commencing hormone therapy.

The use of intermittent hormone therapy has become increasingly popular in patients with less advanced disease. Although the benefits of intermittent therapy are less proven, it clearly improves quality of life in patients with less advanced disease who are destined to use hormones for very long periods. The aim of this therapy is to depress PSA to undetectable levels, wait until it rises again to a predetermined level (such as 10 ng/mL), then commence a further pulse of hormones. This approach gives patients longer periods free of side effects of hormone therapy, such as impotence, depression, lethargy and osteoporosis.

How should hormone therapy be monitored?

Hormonal therapy is best monitored by regular measurement of PSA levels. To assess effectiveness in suppressing testosterone, a serum testosterone can be used and, if not completely suppressed, an antiandrogen can be added. A combination of castration (medical or surgical) and antiandrogen therapy may be used to block both testicular and adrenal androgen

activity. Since the results of major trials have recently become available, enthusiasm for this combination has decreased, but it still tends to be used in young men with early metastatic disease.

How should side effects of hormone therapy be managed?

The side effects of hormones must be managed individually (see Table 2). Hot flushes may be treated with cyproterone, clonidine (Catapres 100) or oestrogen; lethargy may be improved by giving hormones intermittently. Osteoporosis may develop in patients destined to use hormone therapy for long periods; in this group, bone density should be checked at 12 months and therapy such as intravenous or oral bisphosphonates should be used if significant demineralisation is present.

What can we do when hormones no longer work?

When hormone therapy fails, most treatment is palliative. Serum testosterone should always be checked to ensure hormone therapy has been achieving castrate levels of testosterone. Therapeutic options include:

- localised radiotherapy or strontium-89 (Metastron) radiotherapy to painful metastatic deposits
- second-line hormone therapy
- chemotherapy – cyclophosphamide (Cycloblastin, Endoxan-Asta), mitozantrone hydrochloride (Mitozantrone Injection, Novantrone, Onkotrone), docetaxel (Taxotere)
- corticosteroids and pain relief.

A team approach to palliation is important to provide maximal quality of life in men who have hormone refractory cancer, and may include antidepressants, psychological support and hospice services. Promising new approaches include gene therapy, antiangiogenesis drugs such as thalidomide, immunological approaches, and growth factor blocking drugs.

Table 2. Treating side effects of hormone therapy

Hot flushes

- Cyproterone acetate (Androcur, Cyprone, Procur), clonidine (Catapres 100) or oestrogen

Lethargy

- Intermittent hormone therapy

Breast swelling

- Avoidance of antiandrogen
- Radiotherapy to the breast

Impotence

- Intermittent hormone therapy
- Sildenafil (Viagra) or penile injections
- Use of antiandrogens

Depression

- Intermittent hormone therapy
- Varying hormones

Abnormal liver function tests

- Stopping antiandrogens

Osteoporosis

- Bisphosphonates (oral or intravenous)
- Intermittent hormones

Rising PSA level despite hormones

- Serum testosterone check
- Possible referral to a medical oncologist

Conclusion

It is mandatory to tailor therapy for prostate cancer to the individual. Modern treatments, including newer surgical techniques and improved conformal delivery of radiotherapy, have resulted in a significant decrease in side effects and improved outcomes. Further knowledge about biochemical markers, the results of new and improved techniques and more established results of known treatments will help us to individualise treatment, resulting in better control of the disease and fewer side effects. **MT**

Part 1 of this article discussed the issues and controversies involved in screening and diagnosis for prostate cancer.

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