



Gillian Duchesne

Localised prostate cancer

Current treatment options

Background

A number of options are available to treat localised prostate cancer, with different side effect profiles, effect on quality of life and social costs.

Objective

This article outlines the grading and staging of localised prostate cancer and explores the role of each of the treatment options currently available.

Discussion

Treatment selection in localised prostate cancer depends on life expectancy and comorbidities, risk adapted assessment and patient preference. Risk assessment depends on the grade, stage and prostate specific antigen. Options for treatment of localised prostate cancer include active surveillance, radical prostatectomy, curative external beam radiation therapy and brachytherapy. Androgen deprivation therapy in combination with radiation therapy has been shown to increase survival in men with high and high/intermediate risk of occult metastases. Survival rates are essentially equivalent for each modality and are over 90% at 10 years and over 75% at 15 years.

Keywords: prostatic neoplasms/treatment; prostatectomy; radiotherapy



Prostate cancer is the most commonly diagnosed cancer in men, with over 19 000 cases diagnosed in Australia in 2007.¹ The majority of men have minimal or no local symptoms, and have disease localised to the prostate or immediately surrounding tissues (locally advanced), determining the T stage (*Figure 1*).² Nodal and distant metastases represent advanced disease. This article focuses on localised prostate cancer; treatment of advanced disease is beyond the scope of this article.

Treatment decisions

Decisions around treatment for localised prostate cancer are based on life expectancy and comorbidities, risk adapted options and, importantly, on patient preference for procedure type, potential long term side effects and overall quality of life.³

Risk assessment depends on the grade, stage and prostate specific antigen (PSA). The histological grade, or Gleason score, is determined from the morphology of the glandular components of the biopsies.⁴ Two numbers are reported, representing the major and minor patterns seen on histology, and scored from 1–5 representing low to high grade morphology. These numbers are then added together to give a score, eg. Gleason 3 and 4 = 7. A commonly used risk grouping is⁵:

- low risk: T1 or T2a, with Gleason score ≤ 6 ,⁴ PSA ≤ 10 ng/mL
- high risk: T3, or Gleason score 8–10 or PSA > 20 ng/mL
- intermediate risk: those whose T, Gleason and PSA scores fall between the high and low risk values described above.

Calculators of individual risk are now available. However, these generally need to be supported by a clinical discussion to help the patient to interpret the information correctly and make an informed decision based on their individual risk.⁶

Treatment options

Active surveillance

Some patients with low grade (Gleason score ≤ 6) and low volume disease detected on biopsy will never progress to a higher stage or grade. These patients may be suitable for active surveillance



under the care of a specialist. Schedules may vary, but this generally involves a program of quarterly PSA monitoring to detect a PSA doubling time of less than 3 years and planned repeat biopsies at 6–12 months from diagnosis (and thereafter 3–4 yearly), with the aim of early intervention for those who progress.

With careful selection, about 70% of men will avoid treatment for 5 or more years,⁷ although the risk of prostate cancer death may become unacceptable if continued beyond 10–15 years. For this reason, this option may be inappropriate in younger men. If an active surveillance program is to be recommended, the man must agree to an ongoing surveillance schedule with repeated biopsies. The term 'watchful waiting' is not synonymous with active surveillance, and relates to the care of patients with comorbidities and an incidental diagnosis unlikely to affect their survival.

Radical prostatectomy

Radical prostatectomy is generally offered to younger, fitter men because the risk of incontinence with this procedure increases with age. It can be performed via an open retropubic approach, or laparoscopically with or without robotic surgery.⁸ The latter two options have shorter hospital stays and more rapid recovery than open surgery.⁹ The side effect profiles are essentially the same (*Table 1*).¹⁰

Standard surgical risks such as infection, bleeding and thromboembolism apply. Urinary continence can improve for up to 1 year after surgery; major problems are rare and options such as artificial sphincter placement are available. Ongoing erectile function depends on preserving the neural plexus around the prostate through nerve sparing techniques. Phosphodiesterase type 5 (PDE5) inhibitors have limited efficacy after prostatectomy; prostaglandin penile injection or penile prostheses are alternative approaches. In some high risk patients, postprostatectomy radiotherapy may be required to sterilise the surgical bed, although the optimal timing is still under investigation.¹¹

Curative external beam radiation therapy

Currently available techniques are:

- three dimensional (3D) conformal radiation therapy
 - intensity modulated radiotherapy, and
 - image guided radiotherapy,
- with tomotherapy and volumetric therapy becoming available. Radiation therapy is suitable for all fit men with localised or locally advanced prostate cancer, although it tends to be favoured for the older patient, predominantly because of the small risk of late radiation induced second malignancies (about one in 220).¹² Radiation therapy is an outpatient treatment, delivered 5 days a week for up to 8 weeks. The patient experience of the treatment is similar to a diagnostic scan, and attendance takes about 30 minutes

each day. Side effects are either acute, those which happen at the time, related to radiation effects on proliferating tissues; or late, which can occur months or years after treatment and are likely to remain (*Table 2*).

Brachytherapy

Radiation can be delivered directly into the prostate by transperineal implantation of either permanent radioactive seeds (usually iodine-125, low dose rate), or with a temporary implant (high dose rate brachytherapy).¹³ The seed implants are restricted to men with very low risk of extracapsular cancer extension because the radiation range is very short. The key advantage is that radiation dose to surrounding tissues is low, and long term local side effects are potentially less than with other forms of radiation.

The procedure is performed as a day case or with an overnight stay. Most men experience urinary bother (frequency, hesitancy) from swelling of the prostate for several months after treatment, which gradually subsides as the radiation is expended. There is a risk of urinary retention but exclusion of men with existing prostatic symptoms reduces this risk. Radiation protection is not a major issue,

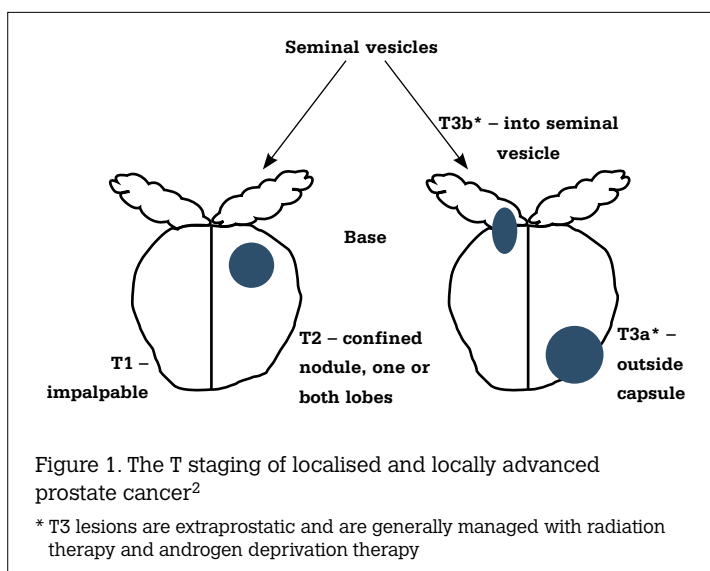


Table 1. Complication rates with radical prostatectomy¹⁰

Complication	Estimated risk
Erectile dysfunction	30–100%
Gastrointestinal effects	Less than 15%
Urethral stricture	Up to 10%
Urinary incontinence – any	Up to 70%
Urinary incontinence – severe	0–5%
Retrograde ejaculation	All

Note: Immediate postoperative complications as for any major surgical procedure (eg. bleeding, thromboembolism)



Table 2. Complication rates with radiation therapy

System	Acute	Late/ongoing
Rectal function		
Bowel frequency	Grade 1: 40%	Grade 1: 30%
Rectal bleeding	Grade 2: 40%	Grade 2: 10%
Pain	Grade 3: 10%	Grade 3: <3%
Urinary function		
Frequency and nocturia	G1 and G2: 80% G3: 10%	G2: 40% G3: <3%
Hesitancy/(retention)	G1 and 2: 50% G3 (retention): 5%	Uncommon
Haematuria	G1 and 2: <10%	G3: <3%
Stricture	None	Rare except after BT: 10%
Incontinence	Rare	0–5%
Erectile function*		
Prior erectile dysfunction	Variable	Impotence usual
Good prior function	Usually maintained	Age dependent, ranges from 30–70% reported; PDE5 inhibitors can be helpful
Dry ejaculate		Usual
Haematospermia		<20%

Notes: Severity of grading: Grade 1: mild, no intervention required; Grade 2: moderate but conservative measures are generally effective; Grade 3: requiring active intervention (eg. argon laser therapy for rectal bleeding)

* About 10% of men on androgen deprivation therapy maintain erectile function. Combined ADT and RT is a significant predictor of subsequent erectile dysfunction, especially with increasing age

ADT = androgen deprivation therapy; BT = brachytherapy; RT = radiotherapy

however men should avoid close contact with children and pregnant women for 2 weeks after implantation. Temporary brachytherapy requires hospitalisation for 2–3 days, during which the patient confined to bed with a perineal template through which several intense treatments are given with a removable radioactive source. It is usually combined with external beam radiation therapy (EB-RT) as a means of achieving very high radiation doses in the prostate.

Androgen deprivation therapy

A number of randomised trials have shown a survival benefit to men with high and high/intermediate risk of occult metastasis at initial presentation when androgen deprivation therapy is used in combination with radiation therapy.^{14,15} This is achieved using a potentially reversible luteinising hormone releasing hormone (LHRH) agonist. The

optimal duration of treatment is still under investigation, but is likely to be between 6 months and several years depending on the risk grouping.

Side effects such as menopausal symptoms, impotence, metabolic syndrome, diabetes and cardiovascular disease, neuropsychological effects and loss of bone and muscle density must be balanced against the potential benefit for each individual man. No benefit has been shown in combination with surgery, probably because surgical series have tended to include lower risk patients.

Other treatments

Other treatment approaches such as cryotherapy and high intensity focused ultrasound (HIFU) have yet to establish their roles in the curative armamentarium.

Survival rates

With current surgical and radiotherapeutic techniques, 10 and 15 year survival rates are equivalent for each modality at over 90% and over 75% respectively,¹⁶ depending on risk grouping. Prostate cancer can be a very indolent disease and late relapses with recurrent PSA elevation are not uncommon beyond 5 years. The median duration from PSA relapse after radical prostatectomy to clinical progression can be as long as 8 years, with median time to death a further 5 years.¹⁷ Relapse is most commonly detected through a rising PSA after post-treatment nadir (undetectable after surgery, preferably less than 1 ng/mL after radiotherapy).

Management is then essentially palliative with androgen deprivation, although the optimal time to start treatment (to balance side effects against potential benefit) is still under investigation.¹⁸ These men can live for a number of years before clinical recurrence is seen, and indeed, clinical recurrence may never happen.

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