EARLY PROSTATE CANCER: OVERVIEW

Prostate cancer is primarily a disease of older men with a slow natural history. Many older men will develop prostate cancer, but the majority will die without the cancer becoming apparent. There is however a subgroup of prostate cancer which is more rapidly progressive and responsible for cancer-related death, these men suffering from and dying prematurely of prostate cancer. Even in this group, prostate cancer progresses relatively slowly, allowing opportunity to consider the treatment options and to plan for treatment.

It may be difficult at the time that curative treatment is possible to determine whether an individual person is destined to develop significant (rather than silent and insignificant) prostate cancer. PSA testing identifies men with prostate cancer early in their disease course, and there is therefore considerable lead time before onset of clinical disease. Our understanding of prostate pathology has changed, and aspects of the treatments have changed, and continue to change. Predicting prostate cancer progression is difficult and may only be determined in some men based on observation over a period of time, differentiating progressive from indolent prostate cancers.

When considering prostate cancer treatment, there remain a number of management options, each with its relative merits and disadvantages. Up-front earlier treatment has potential treatment side effects, and should be considered weighed against other potential health issues, life expectancy and goals of care.

Men over 70 years, and men with other significant health problems, and slower growing tumours should consider carefully the risks of curative treatment and are probably better choosing conservative management.

Fit, younger men with faster growing tumours are more likely to benefit from curative treatment for prostate cancer, but must decide between surgery and radiotherapy, and the relative side effects. Fit younger men appropriate for radical treatment but with “super-early” cancers (small volume on biopsy, low and intermediate grade prostate cancers and PSA below 6) should still consider active surveillance, delaying radical treatment until prompted by MRI scan or change in cancer grade and cancer volume on repeat biopsies, PSA rise, or change of rectal examination findings.

There are currently 3 primary management options for early prostate cancer:

1. Radical prostatectomy = surgery to remove the prostate and the prostate cancer
2. Radical radiotherapy = radiotherapy to destroy the prostate cancer.
    a. External beam is radiation delivered from the outside, focussed onto the prostate
    b. Brachytherapy is radioactive seeds or rods implanted into the prostate
3. Active surveillance (= delaying radical surgery / radiotherapy until the cancer is showing signs of progression) **or** watchful waiting / delayed hormone manipulation (= no treatment until the cancer has advanced and is causing symptoms or PSA is rising rapidly). Medication to block testosterone or chemotherapy is then given to cause the cancer to regress and this may be an effective long-term management.

The decision in favour of a particular therapy is on the basis of:

1. current life expectancy
2. likelihood of death or symptomatic disease from prostate cancer, considering biopsy grade, cancer volume and PSA
3. likelihood of cure from radical treatment
4. side-effects of treatment

1) Life expectancy and prostate cancer progression:

Curative treatment and it's potential treatment side effects should be weighed against other potential health issues, life expectancy and goals of care. Life expectancy can be estimated from age, other medical problems and longevity in the family. nzRISK https://nzrisk.com is an on-line pre-operative risk prediction tool that has been developed and validated for patients in New Zealand over the age of 18, to help patients and doctors balance benefits and risks of treatment.

Most early and low grade prostate cancers do not become clinically apparent until at least 10-15 years after biopsy diagnosis. Almost all ISUP 1 (Gleason 3+3) prostate cancer will remain indolent and clinically inapparent indefinitely. Therefore most patients with small volume, intermediate grade cancer and low PSA, whose prostate cancer is unlikely to progress, should consider active surveillance, delaying radical treatment, watching for cancer progression. Furthermore, patients whose prostate cancer could successfully be managed with hormone treatment alone should avoid more radical treatments.
It appears that MRI scan may identify more clinically significant cancers and this is becoming an increasingly useful investigation for treatment planning.

2) Benefits of treatments:
Radical therapies aim to cure. Currently, radical treatment is either surgery or radiotherapy, rarely both. Chemotherapy is reserved for suitable patients with advanced prostate cancer.
There is some evidence that radical surgery provides a cancer-specific survival advantage for some patients compared with hormonal manipulation/watchful waiting. The potential for over-treatment, and treatment-related side effects, is well recognised however, if all patients with low risk prostate cancer are managed with radical treatment. As with many cancers, not everyone can be cured despite radical treatment, even at an early stage of disease. The likelihood of cure is guided by imaging, biopsy results, PSA and examination findings. Patients with small volume biopsy Gleason score 7 or less prostate cancer (ISUP 1 and 2) and with impalpable disease fare better; patients with high biopsy Gleason score, high PSA and more than 66% of biopsies with prostate cancer should consider carefully whether the relatively small likelihood of cure outweighs the risks of radical treatment. A rapidly rising PSA prior to diagnosis makes cure less likely with radical treatment alone.
There is no consensus on whether surgery and radiotherapy are equivalent at achieving cancer cure, and in the main the choice is based on factors other than the cancer itself, such as patient age and comorbidities. Radiotherapy may be more suitable for locally advanced prostate cancer in older patients, and surgery more appropriate for organ-confined disease in younger patients. Surgery removes only the prostate, and may be considered where investigations indicate a high likelihood the cancer is contained within the prostate. External beam radiotherapy is preferred where there is a greater chance the cancer has extended into the tissues immediately neighbouring the prostate.
Almost all prostate cancers grow under the influence of testosterone. Hormonal manipulation removes this stimulus, resulting in prostate cancer regression for a variable length of time, before the cancer recurs. There is little evidence that hormonal manipulation started early is better than if delayed until PSA rises significantly or symptoms occur. This delayed treatment is referred to as watchful waiting and quality of life is generally better with delayed treatment than in the ‘early hormone treatment’ group.
Hormonal manipulation, early or late, may achieve prolonged remission of prostate cancer.

3) Side-effects of treatment:
There are few adverse effects of **active surveillance** and **watchful waiting** for early stage low risk prostate cancer, other than the need for follow up investigations including prostate biopsies**.**

Hormonal manipulation blocks serum testosterone (androgen deprivation therapy) resulting in hot flushes, reduced energy and vigour, impotence and reduced sexual interest, breast tenderness and swelling, and loss of body hair. Patients suffer from osteoporosis and there is excess cardiovascular disease and risk of myocardial infarction. Intermittent androgen deprivation therapy is a variation on this treatment, tailoring dosing according to PSA, to allow holidays from treatment-related side effects.

Radical prostatectomy is the surgical removal of the prostate, rejoining the bladder to the urethra. Whilst it is a major procedure, it is well tolerated and hospital stay is <4 days. The operation is performed through a lower abdominal incision. A laparoscopic and robotic approach has been used, but has not demonstrated significant advantages over the open procedure. The rate of significant complications at the time of surgery is <10%, blood transfusion 5%, and death 0.5%. Long-term side-effects, which are more common in older men, include urinary incontinence <10% and erectile dysfunction <80% (40% are potent with oral impotence treatment). There are no adverse effects that accrue over time. Effective medical and surgical treatments are available for both incontinence and impotence.

Radical radiotherapy is the destruction of the prostate and cancer with high intensity radiation. It is often combined with a period of hormonal manipulation. Radiotherapy may be delivered by external beam daily, typically over 6 weeks, by implantation of radioactive seeds or rods into the prostate (brachytherapy), or a combination of the two. Whilst radiotherapy is generally well tolerated initially, at the time of treatment, adverse effects accumulate over years post-radiotherapy. These result from radiation damage to neighbouring tissues. Significant radiation effects on the bladder occur in 10% of patients, causing incontinence, bloody urine, irritative bladder symptoms, and when severe, a small capacity rigid bladder. Significant radiation effects on the rectum and intestines occur in 10%, causing bloody mucous diarrhoea, altered bowel habit and soiling. Impotence occurs in 40%. In the long-term, there is a risk of developing non-prostate cancers secondary to the radiation.

In the event of local cancer recurrence after radical prostatectomy, without metastases, it is possible to have salvage radiotherapy to treatment the recurrence.
Surgery following radiotherapy, for cancer recurrence or other symptoms, often has excessive side effects and potential for complications and should be approached with caution.

Comparisons between specific aspects of watchful waiting, radiation and surgery show:

- the majority of patients, having decided on a treatment, remain happy with that decision and would choose the same treatment again. Overall quality of life seems similar between watchful waiting, surgery and radiotherapy patients.
- urinary dysfunction is more frequent in surgical patients, but overall is a more severe problem in the radiotherapy group
- patients managed with watchful waiting have significantly lower rates of urinary incontinence and erectile dysfunction than either surgery or radiotherapy patients
- radiotherapy patients report worse bowel function and bother than patients managed with watchful waiting or surgery
- sexual dysfunction is more frequent in surgical patients, but improves over time, whereas this deteriorates over time in radiotherapy patients, with equal potency rates equal in each group at 3 years post-treatment.
- there is a psychological burden for patients with watchful waiting of the potential for untreated prostate cancer to progress, that impacts on quality of life