**Localised Prostate Cancer**

*Individualised Management Strategies*

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In the current era where prostate-specific antigen (PSA) screening is widespread, more prostate cancers are being detected; the majority (approximately 90%) of them are early stage and clinically localised. Currently, after colon and lung cancer, prostate cancer is the third most common cancer in Singaporean males. According to the Singapore Cancer Registry, there has been a four-fold increase in the number of prostate cancer cases locally between 1968 and 2002. The major dilemma in the management of a newly diagnosed localised prostate cancer is deciding between the many treatment options available.

The most common questions patients with clinically localised prostate cancer ask of their physicians include: ‘What are the treatment options?’ ‘Which is the best or right treatment for me?’ and ‘Are all treatment options just as effective?’.

The current options available for treating early stage (T1/T2) clinically localised prostate cancer include expectant management (ie, active surveillance and watchful waiting), radical prostatectomy, radiation therapy, and energy ablative therapy such as cryotherapy and high intensity focused ultrasound (HIFU). There is currently a paucity of high-level evidence and lack of consensus even amongst experts about the optimal treatment for localised prostate cancer. Indeed, the burden typically falls on the primary physician to help patients find the 'right' answer as to which treatment is optimal for them. This article will discuss the prime considerations when considering treatment and the current management options available.

**What Factors are Important?**

In general, most early prostate cancers have a long time course and low cancer-specific mortality. Therefore, the management recommendation should take into consideration the patient’s life expectancy and overall health. A life expectancy of >10 years is commonly used as a benchmark to determine the benefit of treatment. The disease characteristics that predict for risk of cancer recurrence or progression are also important when deciding therapeutic options.

One of the most commonly used risk stratification methods developed by D'Amico et al (1998), take into account the initial PSA level, Gleason sum (grade), and the clinical stage of disease to classify men into low-, intermediate- and high-risk groups [Table 1]. Other tools such as the Kattan nomogram and Partin tables have also been used to predict the probability of organ-confined disease and to guide therapy decisions. The potential risks of side effects need to be weighed against the benefits of the various treatments. Finally, patient preference and potential quality of life issues such as urinary bother, potency and rectal symptoms should be discussed before deciding on therapy.

**Active Surveillance and Watchful Waiting**

Active surveillance means subjecting patients with localised prostate cancer who are most likely to be safely watched to observation for a period of time, and then for treatment when necessary. In other words, it is not ‘no treatment’ but rather ‘deferred treatment as necessary’. While there is no uniform consensus on inclusion criteria and monitoring parameters, most active surveillance protocols have similar approaches. They include:

1. selecting appropriate patients with low-risk localised prostate cancer;

| Table 1. Risk stratification of clinically localised prostate cancer. |
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| Clinical Stage | PSA (ng/ml) | Gleason sum |
| Low risk | T1c-T2a | ≤10 | ≤6 |
| Intermediate risk | T2b | 10-20 | 7 |
| High risk | T2c | ≥20 | 8-10 |
2. reassuring and educating the patient;
3. close monitoring with periodic PSA measurements, physical examination including digital rectal examination and repeat prostate biopsies; and
4. treat with curative intent if the prostate cancer develops more aggressive features but are still amenable to definitive therapy.

The rationale for this approach stems from the growing concern of the over-detection and overtreatment of prostate cancer. Epidemiologically speaking, a real increase in cancer rate should be accompanied by an increase in death rates. Yet, in many countries (e.g., USA and some parts of Europe), the mortality rates for prostate cancer has remained relatively stable even though the rate of diagnosis has sharply increased over the last few decades. This suggests over-diagnosis. Worldwide autopsy data has shown the presence of prostate cancer in about one third of men (up to 70% in US men) between 60-70 years of age and about 31-58% in men between 70-80 years of age (up to 83% in US men). In spite of this, the number of men who actually die from prostate cancer remains low. Active surveillance gives the benefits of avoiding treatment of insignificant cancer and the side effects of treatment. However, it does have potential limitations such as the patient being chronically anxious over an ‘untreated’ cancer, having to undergo multiple periodic examinations and tests, and the concern of under-detecting a significant cancer resulting in the window of opportunity for cure being missed.

The typical patient who may benefit from active surveillance is one who fits the D’Amico criteria for low-risk disease and has low volume of disease found in his prostate biopsy (e.g., fewer than three positive biopsy cores or less than 33% of total cores, with no core having >50% involvement, in an adequately sampled prostate biopsy, as described by Epstein et al.). A common protocol is to have three-monthly PSA testing and physical examination, and a repeat prostate biopsy within the first year. If no adverse features are seen after two years, the interval between follow-ups may increase and repeat biopsies are done at three- to five-year intervals. In addition, patient age, family history of prostate cancer, and medical co-morbidities should be taken into account when counselling and selecting patients for active surveillance.

Watchful waiting generally refers to patients who are observed, and treated only when symptoms or metastases occurs (usually asymptomatic men with limited life expectancy and have high grade cancers).

Radical Prostatectomy
Radical prostatectomy for localised disease has been shown, with high level evidence, to have advantage in terms of decreased rate of developing metastases and increased survival in comparison to watchful waiting. Its long-term efficacy as a therapeutic modality is well established. However, there is still a lack of level-one evidence of its benefit in comparison to other modalities. It is usually offered as a definitive procedure to reasonably fit men with localised prostate cancer and have more than 10 years of life expectancy. One distinct advantage of choosing this modality of treatment over others is that it allows for accurate pathologic staging. The issue with prostate needle biopsy is that it is not completely accurate and it is estimated that one third of patients who undergo radical prostatectomy may experience a significant increase in disease grade. As all pre-treatment risk prediction methods place a significant weightage on biopsy grade, under-staging is indeed always a possibility. Another advantage is that additional therapy (such as radiation) can be easily added and has shown benefit, if pathology showed upstaging.

The downside to radical prostatectomy is that it involves surgical and anaesthetic risks, and requires a recovery period of two to four weeks. Specific potential post-operative complications can include incontinence (usually stress incontinence) at about 5-20% overall, erectile dysfunction in about 50% at five years, bladder neck contractures and strictures, lymphoceles, and rarely, rectal injury.

One advantage of radical prostatectomy, however, is the possibility of nerve-sparing surgery, which, when added to medical therapy, may improve potency rates compared to other modalities.

In recent years, robotic-assisted laparoscopic radical prostatectomy has gained popularity worldwide. The potential advantages to the patient include less blood loss, less pain, shorter hospital stay and better cosmesis. The benefits to the surgeon include improved ergonomics, 3-D vision and the ease of using more manoeuvrable robotic instruments compared to conventional laparoscopic prostatectomy. However, one major downside is the cost. Conventional laparoscopic prostatectomy has gradually fallen out of favour due to its steep learning curve and long operating times.

Radiation Therapy
Radiation therapy to the prostate is another commonly used modality for treating localised prostate cancer. It can be delivered by external beam, via interstitial seeds (brachytherapy), via temporary radioactive implant (high dose rate brachytherapy, HDR) or their combinations. The development of better tumour-targeting approaches such as 3-D conformal radiation therapy (3DCRT) and intensity-modulated
Radiotherapy (IMRT) has enabled increased therapeutic doses to be delivered to the prostate while decreasing side effects to adjacent tissues. External beam radiation as single therapy has been used to treat low-risk prostate cancers, and, when in combination with androgen deprivation therapy, survival benefit has been shown in higher risk disease. Brachytherapy is mainly used for low-risk disease, and can be combined with external beam radiation for higher risk disease.

The choice of external beam radiation therapy over other modalities has benefits including avoidance of major surgery and hospital stay. However, it requires daily treatments for up to eight weeks. Specific potential risks can include skin reactions, incontinence, erectile dysfunction in about 50% at five years, bladder irritation (such as urinary urgency, frequency, retention and discomfort) and rectal problems (such as pain, diarrhoea, bleeding and urgency). Brachytherapy and HDR require a one-time day surgical procedure of placing prostatic implants percutaneously through the perineum. They tend to have more, but generally tolerable, urinary irritation and similar erectile dysfunction rates compared to external beam radiation therapy. HDR is a relatively newer modality and long-term data is still pending. Other disadvantages of radiation therapy include the inability to provide accurate pathological staging and limited options for salvage therapies or salvage therapies having high complication rates if the disease does recur.

Other forms of radiation therapy such as proton beam therapy and stereotactic body radiotherapy are still not well established for the treatment of prostate cancer.

**Energy Ablative Therapy**

Energy ablative therapies such as cryotherapy and HIFU have been offered as minimally invasive therapy options for localised prostate cancer. Cryotherapy involves placing cryoneedles into the prostate percutaneously through the perineum, and using controlled freeze-and-thaw cycles to destroy prostate cancer cells. HIFU delivers a high energy ultrasound beam via a transrectal probe focused at a specific location of the prostate, and destroys tissues with rapid heat elevation, essentially ‘cooking’ the prostate. The appeal of these modalities is that they are minimally invasive one-time day surgery or outpatient procedures which can be repeated if necessary, and do not preclude alternatives such as radiation therapy or radical prostatectomy. Both modalities have been investigated for use in the setting of focal therapy of prostate cancer.

Cryotherapy has also been used as a modality for salvage treatment of locally recurrent prostate cancer after initial radiation therapy. There is, however, still limited long-term data to determine the impact of these modalities on prostate cancer survival, and their side effect profiles are still being evaluated with newer generation devices. The use of cryotherapy is more prevalent in the US, while HIFU is more commonly used in Europe.

**Conclusions**

There are currently many treatment options available for the management of localised prostate cancer. As there is no single ‘best’ option for all men with localised prostate cancer, management should be individualised, where patient's life expectancy, overall health, risk-benefit ratio of treatment, disease risks, quality of life issues and patients’ expectations should be considered before treatment recommendations can be made.

**References**


At the National University Hospital, the available modalities for management of localised prostate cancer include active surveillance protocol, watchful waiting, open or robotic-assisted laparoscopic radical prostatectomy, external beam radiotherapy, brachytherapy, HDR brachytherapy and cryotherapy.

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