Curative Treatment for Prostate Cancer

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**Introduction**

Latest Hong Kong Cancer Registry figures rank prostate cancer as the 6th most common cancer in 2005\(^1\). It was the 4th most common cancer (after lung, colorectum, and liver) and the 7th major cause of cancer deaths among males of Hong Kong in 2005. There has been dramatic rise in recent years, not only in the number of new cases registered (970 in year 2005), but also in the number of deaths (at least 231 in year 2005) dying from prostate cancer.

In the Seventies, the approach to prostate cancer had generally been expectant, and it had once been the belief that there was no reason to do anything after having made sure that the patient can pass water. As evidenced from the above statistics, the statement that ‘patients die with, rather than die of, prostate cancer’ is now questionable, if not obsolete.

**Natural History**

The incidence of prostate cancer has been increasing due to a multitude of factors: improved methods of diagnosis particularly with the wide availability of serum prostate specific antigen (PSA) assay, an ageing population with longer life expectancy, and the general increase in awareness among doctors and lay public. Prostate cancers do progress and metastasise, albeit at a slower rate than other cancers. The natural course of the disease is long, often more than 10 years. These factors together have resulted in an exponential increase in prostate cancer patients presenting with clinical problems, developing symptoms or metastases during their life span.

Observational studies, particularly that of Chodak et al\(^2\), showed that for patients with reasonable life expectancies from other predictors, watchful waiting is associated with a much higher rate of disease progression and mortality from prostate cancer. Surgical therapy gave a 10-year survival of 78%, compared with 34% for men under surveillance as their disease progressed. While managed by watchful waiting, half of the patients with moderately differentiated tumours will have metastases if they survive 10 years, compared with two-thirds of those with poorly differentiated tumours and even 13% of those with well differentiated tumours. The importance and aggressiveness of prostate cancer cannot be denied. An expectant policy can only be deemed indicated for the infirm, unfit and elderly patients.

When tumours are detected by pathological examination of surgical specimens following transurethral resection for a clinical diagnosis of benign prostatic hyperplasia, some patients may have relatively good outcome at 5 years, but those with extensive or less than well differentiated tumours do not. With longer term follow-up, a Johns Hopkins\(^3\) and a Mayo Clinic\(^4\) series have both shown that even those with tumours involving 5% or less of tissue can have disease progression, metastases and die from the cancer.

**Choice of Therapy**

As it is evident that patients with clinically localised prostate cancer have substantial risk of progressing within their expected life span and dying from the disease, those diagnosed with early-stage prostate cancer should be offered treatment with a goal to eradicate the disease.

The choice of the optimal curative therapy is more controversial. Radical surgery and radical radiotherapy remain the mainstay options. It is difficult to compare their relative merits because there is a lack of randomised studies. Variations in patient selection criteria, clinical and biological follow-up data, and in particular definitions of tumour clearance and recurrence, render outcome results not strictly comparable.

**Radical Radiotherapy**

Radical radiotherapy had been considered a relatively safe option due to lesser immediate side-effects. There has yet to be consensus in the assessment of response after radiotherapy: nadir values ranging from 0.5 to 2.0 ng/ml, or simply a stable level of PSA with absence of 2 or 3 consecutive rises above the nadir level, have been suggested. PSA tends to fall slowly after radiation reaching a nadir at a median of 17 months. The definition of PSA recurrence by the American Society for Therapeutic Radiology and Oncology (ASTRO) as three consecutive rises in serum PSA above nadir level is now generally accepted.

Recent developments in radiotherapy include conformal techniques and brachytherapy. Both aim at reducing radiation complications. A retrospective cohort study by D’Amico et al comparing biochemical outcome after various treatment modalities for clinically localised prostate cancer showed that intermediate- and high-risk patients treated with radical prostatectomy or external beam radiation did better than those treated by interstitial radiation\(^5\).
Adjuvant hormonal therapy has been used to improve the results of radiotherapy. An EORTC randomised prospective trial conducted by Bolla et al demonstrated that adjuvant treatment with a LHRH-agonist analogue, when started simultaneously with external beam radiation, improves local control and survival in patients with locally advanced prostate cancer6.

Radical Prostatectomy

Radical prostatectomy, first described by Young in 1905, has been the dominant therapy for organ-confined prostate cancer. Standard surgical approaches have been either perineal or retropubic. Renewed interest in surgical treatment in the early 1980s has been due to a reduction in operative morbidity, particularly since Walsh has introduced the nerve-sparing retropubic technique which preserves potency as well. Latest addition to the surgical armamentarium is the laparoscopic technique, particularly robot-assisted. To date, the majority of radical prostatectomies worldwide continue to be performed by the retropubic approach, be it open, laparoscopic or robot-assisted, as most practising urologists are well trained and familiar with the anatomy of this approach.

What is important other than the surgical technique is the outcome after surgery. Large institutional series have reported a positive margin rate of 16-46%, but this is affected by specimen artifacts and interpretations. Serum PSA should decline to below detectable levels (less than 0.1 ng/ml) within 21-30 days after radical prostatectomy for organ-confined prostate cancer. This PSA nadir or biochemical clearance is generally regarded a better reflection of the absence of residual disease. More recent large series have reported that, at 10 years, PSA recurrence-free rate is 60-70%, metastasis-free rate is 80-85% and cancer-specific survival is 90% or greater. The post-operative complications of radical prostatectomy as summarised in EAU Guidelines (2001) are listed in Table 1.

The idea of giving neoadjuvant hormonal therapy prior to radical surgery to shrink the tumour or improve the outcome might appear attractive. However, two separate studies, by its proponent the Canadian Uro-oncology Group7 and by Soloway et al8 respectively, have categorically concluded that neoadjuvant hormonal therapy produces no difference in biochemical recurrence rate after radical prostatectomy.

Pound et al at Johns Hopkins studied the natural history of progression following radical prostatectomy, and reported a 91% overall cancer-specific survival at 15 years after surgery9. 15% developed biochemical recurrence (increase in PSA level), 34% of whom developed metastatic disease. The median actuarial time to metastasis was 8 years from the time of PSA increase, and the median actuarial time to death was 5 years from having metastases. Radical prostatectomy can be deemed a treatment with curative intent. It should be offered as a treatment option to the otherwise fit, well-motivated men with early-stage prostate cancer, and at least 10 years life expectancy.

Other Therapy

Cryotherapy has been reintroduced for prostate cancer after improvements in the delivery system and development of the percutaneous TRUS-guided, transperineal percutaneous technique. It may have a role in certain cohorts of prostate cancer patients, but longer term results are awaited.

Endocrine therapy is not a curative treatment option for early-stage prostate cancer. Its ‘palliative’ role in the symptomatic patients unfit for curative treatment has to be balanced against its mostly unavoidable side-effects, which have a negative impact on patients’ quality of life. Androgen-deprivation therapy for prostate cancer increases the risk of fracture in men surviving five years after diagnosis10. A further worry is its limited duration of effect. A local study evaluating orchidectomy and LHRH agonist, though in the treatment of metastatic prostate cancer, confirmed that around 50% of patients could become hormone refractory and had tumour progression by 18 months after starting either treatment, similar to findings in the Western population.

Conclusion

Early aggressive treatment provides the only chance to eradicate prostate cancer. Efforts should therefore be made to detect prostate cancer at a curable stage, and to offer patients with reasonable life expectancy effective curative therapy in order to prevent metastasis or recurrence of the cancer. Patients should not be denied curative therapy on the grounds of age alone.

Table 1: Complications of radical prostatectomy

<table>
<thead>
<tr>
<th>Complication</th>
<th>Incidence (%)</th>
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<tr>
<td>Peri-operative death</td>
<td>0.0-2.1</td>
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<tr>
<td>Major bleeding</td>
<td>1.0-11.5</td>
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<tr>
<td>Nerve injury</td>
<td>0.0-5.4</td>
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<tr>
<td>Deep venous thrombosis</td>
<td>0.0-8.3</td>
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<tr>
<td>Pulmonary embolism</td>
<td>0.8-7.7</td>
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<tr>
<td>Lymphocele</td>
<td>1.0-3.0</td>
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<tr>
<td>Urine leak, fistula</td>
<td>0.3-15.4</td>
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<tr>
<td>Slight stress incontinence</td>
<td>4.0-50.0</td>
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<tr>
<td>Severe stress incontinence</td>
<td>0.0-15.4</td>
</tr>
<tr>
<td>Impotence</td>
<td>29.0-100.0</td>
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<tr>
<td>Bladder neck obstruction</td>
<td>0.5-14.6</td>
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<tr>
<td>Ureteral obstruction</td>
<td>0.0-0.7</td>
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<tr>
<td>Urethral stricture</td>
<td>2.0-9.0</td>
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References