Management of early prostate cancer

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Introduction

Management of early prostate cancer is confounded by a number of problems; these include the frequency of very indolent tumours, the imprecision of prognostic models and the lack of trials of sufficient size to provide reliable comparison of alternative treatment modalities. Nevertheless, there is sufficient evidence to construct reasonable and rational treatment guidelines and to inform patients of the advantages and disadvantages of different initial management approaches. This clear, open and honest discussion is the foundation of good medical practice in early prostate cancer and determines the quality of the long-term relationship between doctor and patient.

There is a large discrepancy between the incidence of, and mortality from, prostate cancer and it has been estimated that three out of four prostate cancers diagnosed today will not cause fatality. This is a product of the relatively old age at presentation and the indolent nature of the cancer. Management requires an understanding of the natural history of the disease and this brief review will focus on a discussion firstly of prognosis and then of each of the three main management options: surveillance, radical prostatectomy and radiotherapy.

Prognosis of early prostate cancer

The major factors influencing outcomes in prostate cancer are histological grade, stage and serum concentration of prostate-specific antigen (PSA). The most widely used pathological grading system is that of Gleason; this is based on tumour architecture rather than cytology. In view of the heterogeneity of most tumours the grading is presented in terms of a primary or most prevalent pattern and secondary or next most prevalent pattern, which are summed to arrive at the Gleason score. Since five grades are recognised ranging from 1 (well differentiated) to 5 (poorly differentiated), the Gleason sum score can range from 2 to 10. The importance of grade is illustrated in a report on 767 patients aged 55–74 years at diagnosis who were managed by immediate or deferred hormone therapy [1]. The 15-year disease-specific mortality rate was 4–7%, 18–30% and 60–87% in those patients with Gleason scores of 2–4, 5 and 6–10, respectively.

There is relatively little data on the significance of initial serum PSA or the range of primary tumour stages on outcomes of patients managed by observation; however, prognostic models from large series have emphasised their independent contribution to prognosis in the context of those treated either with radiotherapy or surgery. The proportion of patients diagnosed at the earliest stages of prostate cancer has been influenced by the availability of PSA as a screening test. The incidence of prostate cancer in the USA rose from 100 per 100 000 in 1988 to a peak of 190 per 100 000 in 1992, with the increase confined to those with localised disease. Local tumour staging is based on digital rectal examination [T1, tumour not palpable; T2, organ confined tumour; T3, capsular or seminal vesicle invasion; T4, invasion of adjacent organ such as bladder, pelvic muscle, rectum]. Local T staging is now aided by sensitive magnetic resonance imaging (MRI) techniques [2]. Five year biochemical progression-free survivals after prostatectomy or radiotherapy are reported to be 94–99% for T1 tumours, 74–87% for T2 tumours and 50–60% for T3 tumours [3–5]. Similarly, prognosis becomes worse in patients with higher presenting serum PSA levels. For example, the large prostatectomy series from John Hopkins shows biochemical disease-free survival probability of only 50% at 10 years for those with a presenting PSA >15 ng/ml [3].

These three variables have been found useful for predicting pathological stage (post prostatectomy) and also prognosis following either prostatectomy or radiotherapy. The Partin tables [4], derived from more than 4300 men treated at three different US institutions by radical prostatectomy, can be used to advise patients on the likelihood that a radical retropubic prostatectomy would result in resection of organ-confined prostate cancer and would lead to long-term disease-free survival. They provide a table for a number of different serum PSA ranges. For example, for those with a PSA between 4 and 10 ng/ml, a T1 tumour and a Gleason score of 7, 36–48% are predicted to have capsular penetration and 3–12% lymph node involvement. With presenting PSA >20 ng/ml this category of patient would have an approximately 46% risk of capsular penetration and 14% risk of node involvement.

Prognostic models have also been constructed to predict survival after radical radiotherapy [5]. Our study was based on 517 men with localised prostate cancer treated with neoadjuvant hormonal ablation for between 3 and 6 months, followed by radical radiotherapy to a dose of 64 Gy in 32 fractions. At a median follow-up of 44 months, the analysis of 233 men who had developed PSA failure confirmed that presenting PSA,
histological grade and clinical T stage were independently predictive, allowing construction of a nomogram score for an individual patient by summation of the points score allocated to categories of each of these variables. The total points score then identifies the probability of remaining biochemically disease free at different time points following treatment, as shown in Figures 1 and 2 [5].

Surveillance

At present it remains unclear which patients gain from early radical treatment. It is clear that either radical prostatectomy or radiotherapy can offer a chance of cure if the tumour is localised. However, it is also clear that many patients with either localised or more advanced tumours will not die of the disease and thus the decision to consider an initial conservative approach to management depends upon a balanced view of the tumour prognosis, background health, life expectancy of the patient and patient preference. Randomised trials comparing radical local treatments with surveillance have not been completed and retrospective epidemiological data are clearly influenced by selection for treatment. However, these data suggest a particular benefit for treatment in patients presenting with more poorly differentiated tumours.

Most studies to define the outcome of surveillance in early prostate cancer were initiated before the era of PSA screening. An overview of five large studies [6] emphasised case selection for this management option since 60% of patients had well differentiated cancers. The outcome supported this judgement since 10 year disease-specific survivals were 81% for well differentiated, 58% for moderately differentiated and 26% for poorly differentiated tumours. However, there is no reliable accurate method to differentiate indolent from aggressive tumours and therefore to seek to avoid the toxicities of curative treatments; there is a risk that a proportion of patients who might have been cured will progress. As a defensive reaction there is therefore a tendency internationally towards overtreatment of patients with early disease. A recent approach to differentiate patients with more aggressive disease has been to analyse the rate of change of PSA with time [7]. Between 1995 and 2000, 134 patients with stage T1 or T2 prostate cancer, a Gleason score ≤7 and PSA ≤15 ng/ml were managed conservatively with observation alone and regular blood tests for PSA. PSA doubling times were <2 years in 19 patients, between 2 and 5 years in 46 patients, between 5 and 10 years in 25 patients, between 10 and 20 years in 11 patients, between 20 and 50 years in six patients and >50 years in 27 patients. There was no correlation between PSA doubling time and age, T stage, Gleason score or initial PSA level. The conclusion was that a conservative approach to management was reasonable in patients aged 70 years or older with a Gleason score ≤6, a PSA ≤10 ng/ml and PSA doubling time ≥10 years.

Radical prostatectomy

The most widely used technique is a radical retropubic prostatectomy which involves access through the lower abdominal wall and a retroperitoneal approach. Complications can include blood loss, rectal injury, and post-operative stricture at the anastomosis between the bladder neck and the
urethra. There is a long-term low risk of urinary incontinence and a relatively high risk of impotence. These side effects appear less common in single institution series than in community surveys [8, 9]. A prospective quality of life evaluation of patients treated in 1 of 4 Rotterdam hospitals [10] has suggested that at 12 months after prostatectomy 33% of patients had total urinary control, 51% had occasional dribbling, 13% had frequent dribbling and 3% had no control; 35% were using incontinence pads; 82% did not have spontaneous erections.

Nevertheless there is convincing evidence that radical prostatectomy can be curative in locally confined cancers even when tumours extended beyond the confines of the prostate (pT3) [11] or when poorly differentiated [12]. Additionally the SEER database provided outcome information on more than 59 000 men with localised prostate cancer diagnosed between 1983 and 1993 [13]. Of these, 24 000 were treated by radical prostatectomy and just under 20 000 by watchful waiting. The 10 year survival difference between these two policies was greatest in patients with poorly differentiated disease and there was little difference in outcomes in patients with well differentiated disease. A similar conclusion was reached by a pooled analysis of multiple radical prostatectomy series [14].

Radiotherapy

There has been considerable development of radiotherapy techniques in recent years. For small, good prognosis tumours in patients without large prostate glands and with good urinary function, it has been suggested that radioactive seed implantation techniques confer a lower risk of toxicity. However, there has been no prospective comparison with modern external beam radiotherapy and outcome assessments in non-randomised series have failed to confirm an advantage [15].

External beam radiotherapy can now be delivered using conformal techniques in which individual beams are shaped to conform the high radiation dose contour to the shape of the tumour volume, reducing the dose to the rectum. A randomised trial has shown that conformal techniques reduce the risk of proctitis and studies now also suggest that these techniques allow radiation dose escalation with improvement of cancer control [16, 17].

Acute side effects include proctitis causing rectal discomfort and diarrhoea, cystitis associated with dysuria and frequency, and rarely skin inflammation. The majority of patients suffer mild symptoms but severe or prolonged reactions occur in 1–4% of patients. In the great majority of patients proctitis resolves within 1–2 weeks and cystitis within 4–6 weeks of completing radiotherapy.

Long-term or chronic complications may develop 1–2 years following treatment and though uncommon, they are of more concern to patients. Gastrointestinal complications may include rectal discharge, tenesmus bleeding or stricture. Urinary complications may include chronic cystitis or urethral stricture. Severe long-term complications requiring surgical correction occur in 1–3% of patients [18]. The risk of toxicity is related to technique and dose [19]. Impotence occurs in 30–50% of treated men and seems less common than after prostatectomy [20].
Since three-dimensional conformal techniques of radiotherapy improve tolerance, there has been exploration by a number of groups of dose escalation. For example, Zelefský et al. [21] have shown that a PSA nadir of 1 ng/ml or less occurred in 90% of patients treated to either 75.6 Gy or 81 Gy compared with 76% of patients treated to 70.2 Gy and 56% of patients treated to 64.8 Gy. Additionally, pooled data from 1465 men treated in Radiation Therapy Oncology Group (RTOG) studies have shown that for high-grade tumours a radiation dose ≥66 Gy was associated with a 29% lower risk of death from prostate cancer compared with lower doses [22]. Randomised trials are now confirming these results [23]. It has been shown with the use of sophisticated intensity-modulated radiotherapy techniques that the prostate can be treated to doses between 75 and 81 Gy with a low risk of complication [24].

There is evidence that neoadjuvant or adjuvant hormonal ablation can improve radiotherapy results. Initial hormone therapy may improve tumour control via an additive effect on prostate cancer cytotoxicity, and additionally it allows a reduction in the radiotherapy target volume of 20–50% [25, 26]. The largest phase III trial was conducted by the RTOG in 471 patients with T2–T4 primary tumours, who were treated with combined androgen blockade for 2 months before, as well as during, radiotherapy, compared with a group treated with radiotherapy alone [27]. The improvements were in both local disease control at 5 years (75% versus 64%; \( P = 0.002 \)) and also freedom from metastasis (71% versus 61%; \( P = 0.03 \)).

Long-term androgen ablation is rational in more advanced tumours and a number of randomised controlled trials have suggested improvement of the disease-specific survival [28] or, in the case of the European Organisation for Research and Treatment of Cancer (EORTC) trial, the overall survival [29]. In this trial 415 men with T3/4 tumours or poorly differentiated T1 and T2 tumours were randomised between radiotherapy alone to the prostate and pelvis or to a combined modality treatment with an LHRH agonist commenced at the beginning of radiotherapy and continued for a period of 3 years. At a median follow-up of 45 months there was an improvement in local disease control with combined modality (97% versus 77%), in disease-free survival (85% versus 48%) and also in overall survival (79% versus 52%; \( P = 0.001 \)).

In an overview of RTOG radiotherapy studies [30], four prognostic groupings were identified. The conclusion was that patients in group two, mainly those with bulky T2 or with T3 and moderately differentiated tumours, initial androgen suppression led to survival benefit. For those in group 3 or 4, who had T3 or poorly differentiated tumours, there was a survival advantage for long-term adjuvant hormone therapy.

**Conclusions**

There is considerable controversy over the optimal individual management of localised prostate cancer and more accurate prognostic techniques are required to define the natural history in the individual patient. On current evidence, curative treatments should be offered to men who have a life expectancy of ≥10 years and this should be considered for men with a life expectancy of ≥5 years if the tumour is poorly differentiated [31]. Radical radiotherapy and surgery should be discussed with the patient with information on tumour control probabilities and possible toxicity. Comparisons between these two treatment modalities suggest that there is little difference in disease control [31, 32]. For well differentiated tumours, there is little evidence that treatment will impact on survival, though longer follow-up is required to apply this principle to younger patients. In managing patients by surveillance it is important to distinguish ‘active monitoring’ from ‘watch and wait’. Active monitoring would be followed by curative treatment in those that demonstrate the potential for rapid growth. ‘Watch and wait’ plans for palliation with hormone therapy to be introduced at the time of symptom development.

**References**
