Global update on defining and treating high-risk localized prostate cancer with leuprorelin: an Asian perspective

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INTRODUCTION

This review gives an Asian perspective on current practices in the use of hormonal therapy (HT) to treat high-risk localized prostate cancer. During the development of prostate cancer, genetic changes in the prostate result in a gradual increase in the number of cancer cells. While the cancer is confined within the prostate, the patient can be treated with a variety of therapeutic options, e.g. HT, surgery, or radiotherapy (RT), and has a good chance of his disease being cured. However, in locally advanced disease surgery is not a valid option, and HT or RT-based treatment strategies are generally used.

TRENDS IN PROSTATE CANCER THERAPY

Recent data from the Cancer of the Prostate Strategic Urological Research Endeavor show that radical prostatectomy (RP) is a commonly used primary therapy in many high-risk patients; however, most (>50%) are treated with HT or a combination of HT and RT, i.e. external-beam RT (EBRT) or brachytherapy [1].

The results for high-risk patients, such as those with a Gleason score of 8–10 and a PSA level of >20 ng/mL, who have undergone RP, show that biochemical failure is high and biochemical disease-free survival is low (≤50% at 5 years and =40% at 10 years) [2]. However, this indicates that there are still 40% of patients who do not relapse.

The Japanese Urological Society analysed trends in the treatment of localized prostate cancer in Japan [3,4]. Overall, almost half of men with prostate cancer are treated with HT, regardless of stage; RT is also widely used in high-risk patients. This raises the question of whether initial RP is an effective way to treat high-risk patients.

DETERMINANTS OF RESPONSE TO HT

A retrospective, multicentre study in Japan reviewed the efficacy of HT for localized prostate cancer [5]. The study included 628 men with prostate cancer from seven institutions, 63.5% of whom were treated with combined androgen blockade (CAB; luteinizing hormone-releasing hormone agonists plus an antiandrogen) and 36.5% with medical or surgical castration. CAB treatment was significantly better than hormone monotherapy for disease-specific survival. The results also showed that, even if a patient is classified as ‘high-risk’, a good prognosis could normally be predicted based on certain variables: if their initial prostate-specific antigen (PSA) level was ≤20 ng/mL, their Gleason score was ≤6, and their nadir PSA decreased to ≤0.2 ng/mL within 6 months of HT. In this subgroup of ‘good responders’, any treatment, be it prostatectomy, RT or CAB, is likely to be effective. However, in ‘poor responders’, combined therapies with CAB and high-dose rate brachytherapy are likely to be needed for a clinical response. While HT is effective, it might be associated with a reduction in the patient’s quality of life (QoL) due to adverse effects, e.g. a reduction in sexual function. Results from the analysis of QoL questionnaires completed by men of different ages with prostate cancer found that only sexual function, and not other QoL variables, in men aged 50–59 years appeared to be reduced in men who had HT, compared to age-matched controls.

KEYWORDS

prostate cancer, high risk, leuprorelin, hormone therapy, quality of life, Asia
for NSAA and 64.6% for SAA at 5 years, \( P = 0.005 \).

Patients were stratified into modified D’Amico risk groups: low risk was defined as a PSA level of \( \leq 10.0 \) ng/mL, a Gleason score of \( \leq 6 \), and stage \( \leq T2 \) (110 patients); intermediate risk was defined as those patients falling between low- and high-risk; and high risk was defined as a PSA level of \( > 20.0 \) ng/mL, a Gleason score of \( \geq 8 \) or stage \( \geq T3 \) (376 patients). Both disease-free and PFS were greatest in the low-risk patients (Fig. 1) [5]. Of the high-risk patients, 60% had relapsed after 10 years. However, 40% did not relapse, so the focus of our studies should be on how we can identify this subgroup and treat them accordingly.

Further analysis of this subpopulation was undertaken, and they were stratified according to several variables including initial PSA level (using a threshold of \( \leq 20 \) vs \( > 20 \) mg/mL), Gleason score (\( < 7 \) vs \( 7 \) vs \( \geq 8 \)), T stage (\( < T3 \) vs \( T3 \)), time to PSA nadir (\( \leq 6 \) vs \( > 6 \) months), and PSA nadir (\( \leq 0.2 \) vs \( > 0.2 \) ng/mL). The prognosis was better in patients with a PSA level of \( \leq 20 \) ng/mL, Gleason score \( < 7 \), stage \( < T3 \), time to PSA nadir of \( \leq 6 \) months, and a PSA nadir of \( \leq 0.2 \) ng/mL. The PSA nadir appears to be an important prognostic factor; if it was \( \leq 0.2 \) ng/mL the PFS rate at 10 years was 66.7%, but if it was \( > 0.2 \) ng/mL then this decreased to 0% at 10 years.

The PSA nadir combined with other variables was also analysed. A combination of a PSA nadir of \( \leq 0.2 \) ng/mL and a time to PSA nadir of \( \leq 6 \) months resulted in a good prognosis, with a PFS rate of 79.0% at 10 years. A combination of a PSA nadir of \( \leq 0.2 \) ng/mL and an initial PSA level of \( \leq 20 \) ng/mL also resulted in a good prognosis, with a PFS rate of 76.0% at 10 years. The best combination was that of a PSA nadir of \( \leq 0.2 \) ng/mL and an initial Gleason score of \( < 7 \), resulting in a PFS rate of 91.7% at 10 years. A combination of a PSA nadir of \( > 0.2 \) ng/mL and a time to PSA nadir of \( > 6 \) months resulted in a very poor prognosis, with a PFS rate of 0% at 10 years. The same results were seen with a combination of a Gleason score of \( \geq 7 \) and a PSA nadir of \( > 0.2 \) ng/mL (Fig. 2).

To summarize, after initial CAB therapy, of those patients who responded to therapy and achieved a nadir PSA of \( \leq 0.2 \) ng/mL, 40% (150/376) had a ‘good’ response (defined as a...
Gleason score of ≤6, an initial PSA level of ≤20 ng/mL, or a time to PSA nadir of ≤6 months).

**CHOICE OF THERAPY FOR HIGH-RISK PATIENTS**

Many studies have been undertaken to determine how best to treat patients with high-risk prostate cancer. A randomized, phase III trial undertaken by Bolla et al. [6] showed that a combination of immediate androgen suppression with an LHRH analogue given during and for 3 years after external irradiation (at a dose of 50 Gy to the whole pelvis plus a 20 Gy prostate boost) improved disease-free and overall survival of patients with locally advanced prostate cancer compared with RT alone. Data for a total of 412 patients with T1–2 tumours of WHO grade 3 or T3–4, N0–1M0 tumours and a median age of 71 years were evaluated with median follow-up of 66 months. The 5-year clinical disease-free survival was 40% in the RT-alone group and 74% in the combined-treatment group (P < 0.001); the 5-year overall survival rate was 62% and 78%, respectively (P < 0.001) and 5-year disease-specific survival 79% and 94%.

High-dose rate (HDR) brachytherapy was evaluated in a study in Japan [7]; the PFS in high-risk patients treated with HDR-brachytherapy alone was 79.0%, and in those treated with HDR-brachytherapy plus adjuvant HT this increased to 100% (Table 1).

One approach to treating men with high-risk prostate cancer is to start with neoadjuvant CAB, then once a PSA nadir of ≤0.2 ng/mL has been reached, the Gleason score, initial PSA level and time to PSA nadir should be checked. As has been shown within the subgroup of good responders (those with a Gleason score of ≤6, an initial PSA level of ≤20 ng/mL, or a time to PSA nadir of ≤6 months) it is likely that >75% will not relapse even 10 years after CAB. Therefore, in good responders, we can select any treatment option after discussing with the patients the various options and their impact on quality of life (QoL), e.g. we can stop CAB after 6 months and undertake RP or RT, or we can continue CAB or intermittent CAB. Even if recurrence occurs after RP or RT, CAB therapy is the likely treatment option for these patients. However, ‘poor responders’ should be treated with intensive therapy using CAB combined with HDR-brachytherapy, intensity-modulated RT, EBRT or some form of chemotherapy (Fig. 3).

**QoL**

While HT is effective, it might be associated with a reduction in the patient’s QoL due to adverse effects, e.g. a reduction in sexual function. Satisfaction with everyday life was investigated in 49 men receiving HT for prostate cancer and compared with that in a healthy control group of 150 older men who had an age-related health check in Japan (Mizokami, unpublished data). Answers were recorded using a validated questionnaire, the Androgen Deficiency in Ageing Males (ADAM) questionnaire [8].

In all age groups (50–59, 60–69, 70–79, and >80 years), treatment with HT reduced the ADAM score, suggesting that there was a tendency for the QoL of men who had HT to be better than that of the 150 controls (Fig. 4, Table 2). Only sexual function in men aged 50–59 years appeared to be better in control subjects than in men who had HT.

**CONCLUSIONS**

The results from a retrospective study of primary HT in locally advanced prostate cancer...
cancer show that a good prognosis can be expected if the initial PSA level is ≤20 ng/mL, the Gleason score is ≤6 and the nadir PSA decreases to ≤0.2 ng/mL within 6 months of HT (a good responder), even if this patient is classified as ‘high-risk’. For ‘good responders’, it appears that any treatment, such as RP, RT or CAB, will be effective. Combined therapies with CAB and HDR-brachytherapy are likely to be necessary for treating poor responders. Although the QoL of men with prostate cancer is reduced while receiving HT, analysis of QoL questionnaires completed by men of different ages and with prostate cancer suggest that it is rather better than previously thought.

CONFLICT OF INTEREST

None declared.

REFERENCES


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Abbreviations: CAB, combined androgen blockade; QoL, quality of life; HT, hormone therapy; RP, radical prostatectomy; (EB)RT, (external-beam) radiation therapy; (N)SAA, (non)steroidal antiandrogens; PFS, progression-free survival; HDR, high-dose rate; ADAM, Androgen Deficiency in Ageing Males (questionnaire).