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

Laurent Boccon–Gibod
Department of Urology, CHU BICHAT, University of Paris VII, Paris, France

High-risk prostate cancer can be defined as a cancer that, although clinically localized, will not be cured by monotherapy, whether surgery or radiation, and as a result will require some form of multimodal therapy, which will normally include luteinizing hormone-releasing hormone agonists. High-risk localized prostate cancer can be identified at three specific points during the management of the patient; before starting treatment (based on the profile of some predictive criteria, e.g. pathological features, prostate-specific antigen, PSA, level, and PSA velocity), on pathological evaluation of a surgical specimen taken during radical prostatectomy, or at the point of PSA relapse after radiotherapy or surgical therapy. Within Europe, therapeutic choice in patients identified as high-risk is normally made based on their age and life-expectancy. In those with a relatively long life-expectancy (>10 years) androgen suppression therapy (AST) should form part of a multimodal approach to treatment, but neoadjuvant hormonal therapy should be limited to use in combined hormonal therapy/radiotherapy protocols. AST can also be used to treat patients with PSA relapse. Several studies investigated the relative advantages of giving AST continuously vs intermittent therapy, but there are no notable differences between these approaches. AST monotherapy can be indicated in those patients with a shorter life-expectancy (<10 years), particularly if there are poor risk factors, e.g. a high PSA level (>50 ng/mL) or a short PSA doubling time (<12 months).

INTRODUCTION

This review gives a European perspective on current practices in the use of hormonal therapy to treat high-risk localized prostate cancer. High-risk prostate cancer can be defined as a cancer that, although clinically localized (for example T3–4, N0M0), will not be cured by monotherapy, whether this is surgical or energy based, e.g. external-beam radiation therapy (RT), brachytherapy, cryotherapy, etc., and therefore requires multimodal therapy. LHRH agonists are an integral part of such multimodal treatment. There are three situations in which high-risk, localized prostate cancer can be identified: (i) before starting treatment; (ii) on pathological evaluation of a surgical specimen taken during radical prostatectomy (RP); and (iii) at the point of PSA relapse after energy-based or surgical therapy.

BEFORE STARTING TREATMENT

High-risk prostate cancer can be diagnosed at this point based on the profile of some predictive criteria: pathological features, e.g. extracapsular extension (ECE), seminal vesicle invasion (SVI), and node-positive disease, and the risk of PSA relapse. While these factors might be indicative of high-risk prostate cancer their relevance as surrogate endpoints for cure is currently unclear.

There are several tools that can be used before therapy to help predict the risk of prostate cancer, including Partin tables [1], Kattan nomograms [2] and the risk groups of D'Amico et al. [3]. While these might be useful in the clinical trial situation, they appear to be of less value in assessing the individual patient.

There are several other factors that are predictive of ECE and positive margins, including palpable nodules, a PSA level of >10 ng/mL (and possibly a high PSA velocity; the rate of increase in PSA levels in successive PSA tests over the previous 12 months), a predominant Gleason score of ≥4, half or more of biopsies invaded by cancer, cancer comprising 40–50% of the length of the biopsies (a crude measure of tumour volume), any biopsy totally invaded by cancer, and SVI detected on MRI.

For patients with high-risk, localized prostate cancer diagnosed before therapy there are various therapeutic options that can be used, depending on the patient's age and life-expectancy. For patients with a life-expectancy of <10 years standard therapy comprises androgen suppression therapy (AST) using either medical castration or subcapsular orchidectomy. In addition to the standard of care, other options that can be considered for these patients include intermittent androgen deprivation, nonsteroidal antiandrogen (NSAA) monotherapy, or surveillance with delayed AST, which is probably best reserved for patients with minimal symptoms and a PSA level of <25 ng/mL.

Treatment with intermittent androgen deprivation is reviewed elsewhere in this supplement [Tunn, page 19–22] and so will not be discussed here. Treatment with NSAA (bicalutamide, flutamide or nilutamide) monotherapy has been used with some success in patients with high-risk prostate cancer, but the use of bicalutamide in patients with T3NxM0 disease has been shown to be inferior to castration in terms of survival benefits [4]. Bicalutamide is an effective treatment in patients with locally advanced disease treated with hormone deprivation only, but in low-risk patients it has a negative impact on survival compared with placebo. Thus at present there is insufficient evidence to recommend the use of bicalutamide monotherapy as a standard of care in high-risk patients.

Studies of early vs delayed AST were presented at recent international urology meetings, including the AUA 2006 congress and the European Association of Urology 2006 meeting. They showed that in patients with T2/T3 prostate cancer not amenable to

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For patients with a life-expectancy of less than 10 years the goal of therapy is to achieve a cure and according to the European Association of Urology guidelines the standard therapy should comprise combined hormone therapy and RT. The latter normally comprises three-dimensional conformal radiation at a dose of >75 Gy. The timing and duration of LHRH therapy is variable but it is generally given a month before RT and continued for 24–36 months after treatment. There is also the option of RP with extended pelvic lymph node dissection. This has most benefit in younger patients (<65 years old), particularly those who have significant BPH-related LUTS. However, neoadjuvant AST has not been shown to be of benefit in this situation.

**PATHOLOGICAL EVALUATION OF THE SURGICAL SPECIMEN**

High-risk localized prostate cancer can also be diagnosed based on the adverse pathological features in the specimen taken during RP. For a patient who has ECE, node-negative disease, and positive margins with or with no SVI, RP plus adjuvant radiotherapy gives better biochemical progression-free survival rates than RP alone [6] (Fig. 2), and this is now considered to be the standard of care in these patients.

The investigators undertook a randomized, controlled trial to compare RP followed by immediate external irradiation with RP alone in 1005 patients with PT3N0M0 prostate cancer, and one or more pathological risk factors: capsule perforation, positive surgical margins, or SVI. After RP patients were randomly assigned to a watchful-waiting policy or to immediate radiotherapy (60 Gy conventional radiation delivered over 6 weeks). After a median follow-up of 5 years, the biochemical progression-free survival was significantly better in the irradiated group (74% vs 52.6%; \( P < 0.001 \)). Clinical progression-free survival was also significantly improved \( (P < 0.001) \). As yet these benefits have not been reported to translate into improvements in overall survival.

Other therapeutic options in this patient group are surveillance until PSA relapse or possibly early hormonal therapy. Results after 5.4 years of follow-up of a study undertaken by the Scandinavian Prostate Cancer Group, of bicalutamide or placebo added to standard care, i.e. RP, radiotherapy or watchful waiting, showed that patients with locally advanced disease had better survival with bicalutamide (hazard ratio, HR, 0.68) while those with localized disease had decreased survival (HR 1.47). In patients with localized or locally advanced prostate cancer bicalutamide significantly improved progression-free survival, decreasing the risk of disease progression by 43% compared with placebo (HR 0.57; \( P < 0.001 \)). Patients with locally advanced disease gained the greatest benefits in progression-free survival with bicalutamide (HR 0.40) [7].

Immediate AST after RP and pelvic lymphadenectomy improved survival and reduced the risk of recurrence in patients with node-positive prostate cancer, so this is recommended as the standard treatment in these patients [8]. In that study, 98 men who had RP and pelvic lymphadenectomy, and who had nodal metastases, were randomly assigned to receive immediate AST, with either an LHRH agonist or bilateral orchidectomy, or to be followed until disease progression. After a median of 7.1 years of follow-up, seven of 47 men who received immediate AST had died, compared with 18 of 51 men in the observation group \( (P = 0.02) \). The cause of death was prostate cancer in three men in the immediate-treatment group and in 16 in the observation group \( (P < 0.01) \). At the time of the last follow-up, 36 men (77%) in the immediate-treatment group and nine (18%)...
in the observation group were alive and had no evidence of recurrent disease, including undetectable serum PSA levels ($P < 0.001$).

PSA RELAPSE

The fastest expanding group of patients with prostate cancer is those who have PSA relapse after treatment with curative intent. After RP, PSA relapse is defined as a level of 0.2 ng/mL and rising. After radiotherapy, PSA relapse is defined according to the latest American Society for Therapeutic Radiology and Oncology definition: three consecutive rises from the PSA nadir after treatment, with a minimum value of 0.5 ng/mL [9].

Treatment decisions should ideally be based on an analysis of PSA kinetics. A retrospective, observational, multicentre study by Moul et al. [10] showed no difference in disease-free survival in patients who received early vs late hormonal therapy after PSA relapse after RP (Fig. 3). However, in the subgroup of patients who had poor prognostic features and a short PSA doubling time (PSA-DT) there was a benefit to giving early hormonal therapy. They examined the Department of Defense Center for Prostate Disease Research observational database to compare clinical outcomes in men who had a PSA relapse after RP according to whether that received early or delayed AST, and according to risk stratification. In all, 1352 men who had PSA relapse (PSA after surgery >0.2 ng/mL) were divided into an early AST group in which patients (355) received AST after PSA-only recurrence but before clinical metastasis, and a late AST group for patients (997) who received no AST before clinical metastasis or by current follow-up. The primary endpoint was the development of clinical metastases. Of these 1352 patients, clinical metastases developed in 103 (7.6%). In the overall cohort early AST did not affect clinical metastases but it was associated with delayed clinical metastasis in patients with a Gleason score of >7 or PSA-DT of <12 months (HR 2.12; $P = 0.01$).

As indicated, in cases of PSA relapse the therapeutic choice should be based on PSA kinetics, and it is important to have this information for an individual patient before making treatment decisions that use aggressive therapies.

A study by D'Amico et al. [11] investigated whether a short post-treatment PSA-DT after RP or RT was a surrogate endpoint for prostate cancer-specific mortality (PCSM). Information was compiled for a cohort of 8669 patients with clinical stage T1c-4NXM0 prostate cancer treated with surgery (5918) or RT (2751). After PSA relapse, a PSA-DT of <3 months was significantly associated with time to PCSM and with time to all-cause mortality ($P < 0.001$; Fig. 4). Furthermore, a PSA-DT of <3 months was significantly associated with PCSM (HR 19.6) and could be considered as a surrogate endpoint for PCSM after surgery or RT.

Another recent study by D'Amico et al. [12] showed that the natural history of PSA relapse is a function of PSA kinetics. They undertook a prospective prostate cancer screening study that enrolled, diagnosed and treated 1011 men who had had a RP for localized prostate cancer at Barnes-Jewish Hospital (St Louis, MO, USA) between 1989 and 2002. Whether the level of risk for PSA failure after RP could be identified using information available at diagnosis was evaluated. The study showed that a preoperative PSA velocity of >2.0 ng/mL/year ($P = 0.001$) and a biopsy Gleason score of 7 ($P = 0.006$) or 8–10 ($P = 0.003$) were significantly associated with having a PSA-DT after RP of <3 months. A PSA level of <10 ng/mL ($P = 0.005$), an impalpable cancer ($P = 0.001$) with a Gleason score of ≤6 ($P < 0.001$), and a preoperative PSA velocity of <0.5 ng/mL/year ($P = 0.03$) were significantly associated with a PSA-DT after RP of ≥12 months or no PSA failure. It was concluded that a PSA-DT of <3 months is associated with a preoperative PSA velocity of >2.0 ng/mL/year and high-grade disease. In addition, a subgroup of patients with longer PSA-DTs after RP (≥12 months) might not require salvage RT.

In terms of treatment options for these patients, those with a ‘short’ PSA-DT should probably be offered AST, but whether this is better given continuously or intermittently has yet to be confirmed. The exact definition of ‘short’ is still the subject of debate; should it be <3, <6 or <12 months? Patients who have a PSA relapse might also benefit from cytotoxic chemotherapy, or a combination of AST plus chemotherapy, but there are currently no evidence-based guidelines for this approach.
CONCLUSIONS

Within Europe it is generally considered that for patients with high-risk prostate cancer and a life-expectancy of >10 years AST should form part of a multimodal approach to therapy. However, neoadjuvant hormonal therapy should be limited to use in combined hormonal therapy/radiotherapy protocols. AST can also be used to treat patients with PSA relapse but there appears to be no advantage of giving this continuously rather than intermittently. AST monotherapy might have the advantage of giving this continuously rather than intermittently. AST monotherapy might be indicated if the patient’s life-expectancy is <10 years and there are poor risk factors, e.g. a PSA level of >50 ng/mL or a PSA-DT of <12 months. The role of NSAAs, e.g. bicalutamide, when used as monotherapy in high-risk prostate cancer remains to be defined.

CONFLICT OF INTEREST

None declared.

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Correspondence: Laurent Boccon-Gibod, Department of Urology, Hôpital Bichat, 46 Rue H Huchard, Paris 75018, France. e-mail: laurent.boccon-gibod@bch.ap-hop-paris.fr

Abbreviations: RT, radiation therapy; RP, radical prostatectomy; ECE, extracapsular extension; SVI, seminal vesicle invasion; NSAA, nonsteroidal antiandrogen; PCSM, prostate cancer specific mortality; AST, androgen suppression therapy; PSA-DT, PSA doubling time; HR, hazard ratio.