What’s New in Prostate Cancer: Highlights from Urologic and Oncologic Congresses in 2006

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Abstract
Objectives: This report summarises major new findings in the field of prostate cancer (PCa) presented during the 2006 annual meetings of the European Association of Urology (EAU), American Urological Association (AUA), American Society of Clinical Oncology (ASCO), and the American Society for Therapeutic Radiology and Oncology (ASTRO).
Methods: Urologic experts in the field of PCa selected relevant new findings that were discussed during a closed meeting in September 2006. The key points are communicated in this paper.
Results: There was much discussion about the relevance of Prostate-Specific Antigen (PSA) screening. There seems to be no specific threshold for early detection of clinically relevant PCa. PSA doubling time and PSA velocity may be more reliable to predict the risk of disease progression in patients with PCa. The first randomised controlled trial showed a comparable survival rate and risk of disease progression for external-beam radiation therapy and radical prostatectomy in patients with clinically localised PCa. In patients with advanced PCa, intermittent hormone therapy does not increase the risk of disease progression compared to continuous hormone therapy, while it has less impact on patient’s quality of life. Patients receiving hormone therapy may benefit from an annual single-dose injection of zoledronic acid for the prevention of bone complications. Besides PSA, testosterone levels should be monitored in patients on androgen-deprivation treatment.
Conclusions: Many interesting data in the field of PCa have been presented at this year’s uro-oncologic meetings, which will improve the management of patients with PCa.

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1. Introduction

Prostate cancer (PCa) is the second leading cause of cancer-related deaths among men in Western countries. The annual incidence rates in 2000 ranged between 19 and 55/100,000 men [1]. Due to the ageing of the population, the incidence of PCa will further increase. When evaluating the period of 2000–2003, the median age at diagnosis for PCa was 68 yr, whereas the median age at death due to PCa was 80 yr. Fig. 1 clearly shows that men between 65 and 74 yr of age are at the highest risk of being diagnosed with PCa, whereas men aged 75–84 yr have the highest mortality rate (www.seer.cancer.gov). Stage distribution shows that 91% of the PCa cases are diagnosed at localised or regional stage (ie, diagnosed while the cancer is still confined to the primary site or after the cancer has spread to regional lymph nodes), whereas 5% was diagnosed when the cancer was metastasised (distant stage). There seems to be an absolute (100%) 5-yr PCa-specific survival when patients have localised/regional PCa, compared to only 33.3% when metastases occur (www.seer.cancer.gov). This underlines the fact that early detection of PCa is important.

PCa is already a major health and social problem, and it will become even more important due to the ageing of the population. The management of PCa remains a key challenge for physicians. Efforts are still needed to improve diagnosis and treatment of PCa. Recent progress in the field of PCa has been presented at this year’s meetings of the European Association of Urology (EAU), American Urological Association (AUA), American Society of Clinical Oncology (ASCO), and American Society for Therapeutic Radiology and Oncology (ASTRO). A subset of new data has been selected by urologic experts in the field of PCa and was presented during a closed meeting in Cannes, France in September 2006. This paper summarises the most important findings that were discussed during the meeting in Cannes.

2. Detection and screening

In the era before Prostate-Specific Antigen (PSA), PCa was usually incurable at the time of diagnosis. The introduction of PSA screening has contributed to the earlier detection of PCa in many cases. Currently, major studies in both the United States and Europe are evaluating the potential of PSA screening in the early detection of PCa and its impact on mortality and morbidity [2]. Over the last decade, many centres of excellence have lowered their PSA threshold for prostate biopsy <4 ng/ml to detect more PCa at an organ-confined stage, which increases the risk of PCa-specific survival. However, lowering the PSA threshold substantially increased the number of biopsies and subsequently led to the detection of more clinically insignificant cancers, therefore accentuating the problem of overtreatment [3]. Furthermore, there is an ongoing debate whether low PSA values even correlate with the risk of PCa. During the EAU 2006 annual meeting, the outcomes of a retrospective European study performed between January 1999 and December 2004 on 555 men who underwent a routine eight-core prostate biopsy were presented. The effect of lowering the PSA threshold from 4 to 2.5 ng/ml was investigated, as well as the diagnostic yield of the two PSA cut-off values. Indications for a prostate biopsy were a suspicious digital rectal examination (DRE) or a PSA >2.5 ng/ml. Men older than 75 yr or with a PSA >10 ng/ml were excluded from the study [3]. Overall, PCa was detected in 24.1% of patients. As shown in Fig. 2, a significantly higher percentage of patients was positive for PCa in the group with a PSA value of 4–10 ng/ml compared to the group with a level <4 ng/ml (p <0.001). The authors indicated that the PSA value significantly correlated with the risk of PCa in the range <10 ng/ml with an age-adjusted odds ratio of 1.16/1 ng/ml increase in PSA. PCa detected at a PSA level <4 ng/ml also showed more favourable pathologic features on biopsy (ie, lower Gleason scores) than at the level of 4–10 ng/ml [3]. However, the results supported the notion that there is no distinct PSA threshold available for the early detection of clinically significant PCa. During the closed meeting, this conclusion was supported. Data from the Prostate Cancer Prevention Trial showed that the prevalence of PCa is high even in PSA strata considered absolutely normal (ie, PSA 0–1 ng/ml or 1.1–2.0 ng/ml) [4]. This should be considered during screening for PCa. Furthermore,
the outcomes of this study showed a bias towards a greater detection of high-grade PCa with finasteride compared to placebo [4]. During the discussion it was stressed that the use of PSA thresholds should be handled with care in patients taking finasteride because finasteride significantly lowers the PSA value and reduces prostate size. Another important issue was the implementation of the PSA velocity (PSA-V), which indicates the rate of change in PSA level over time. This may often provide a more detailed picture as to whether the patient should undergo a rebiopsy or not [5].

3. Natural history

Active surveillance followed by selective treatment for those with evidence of disease progression may be chosen for men with favourable tumour characteristics. During the AUA 2006 annual meeting, Master and coworkers [6] reviewed the clinical profiles and outcomes of patients with PCa managed initially with an active surveillance program. The study included 240 patients; inclusion criteria were PSA < 10 ng/ml, Gleason score ≤ 6 (with no pattern of 4 or 5), cancer involvement of <33% of biopsy cores, and clinical stage T1/T2a. Disease progression was defined as an increase in rebiopsy Gleason sum >6, any increase in tumour lesion size or number on transrectal ultrasound, or significant PSA-V changes (absolute PSA or PSA density > 0.15 ng/ml/g) accompanied by increased biopsy Gleason sum. Active surveillance consisted of PSA measurements and DRE every 3–6 mo, rectal ultrasound every 6–12 mo, and a repeat biopsy at 12–24 mo. After an overall mean follow-up of 2.6 yr, an initial mean PSA level of 6.5 ± 3.4 ng/ml was measured. Sixty-three percent (152 of 240) of patients underwent a repeat biopsy at 12 and 24 mo. The overall risk of disease progression at 5 yr was 9.7% for patients meeting all inclusion criteria compared to 31.7% of those who did not. Although no evidence of disease progression was provided, 4% of the cohort chose definitive therapy at a mean time of 1.5 yr of active surveillance. It was concluded that using specific criteria, carefully selected patients with low-risk PCa are good candidates for active surveillance. However, follow-up over a longer period and in a larger number of patients is recommended to evaluate this approach.

4. Biopsy and histopathologic issues

Pathologists have played a crucial role in gathering data on which modern therapy is based and they continue to provide essential information on which surgeons, radiation oncologists, and medical oncologists base their therapeutic and management decisions [7]. During the EAU 2006 annual meeting, Van Der Kwast and colleagues performed a critical central pathologic review of prostatectomy specimens to assess predictors of biochemical recurrence [8]. In this study, as part of the European Organization for Research and Treatment of Cancer (EORTC) trial 22911, 502 patients were assigned to immediate postoperative radiotherapy after radical prostatectomy and 503 patients to a control arm. A total of 552 prostatectomy specimens (280 in control arm and 272 in test arm) from 12 major centres were reviewed by a single pathologist for stage, margins, and Gleason score. Agreement of local pathologists and review pathologist was high (κ = 0.83) for seminal vesicle involvement, but low for extracapsular extension (κ = 0.33) and margin status (κ = 0.45). The overall agreement for extracapsular extension and margin status was low, 57.5% and 69.4%, respectively. Gleason sum, margin status as well as postoperative PSA (>2 ng/ml vs. <2 ng/ml) assessed by the review pathologist were the strongest predictors of biochemical progression-free survival. Based on this retrospective centralised pathologic review a prognostic classification suggests that patients with Gleason >7, positive margins, and postoperative PSA > 2 ng/ml may benefit most from radiotherapy following radical prostatectomy.

5. Radiotherapy

Radiotherapy may consist of external-beam radiation therapy (EBRT), brachytherapy, or a combination of
both. Currently, there are no randomised trials comparing the various radiation techniques with each other or to radical prostatectomy. As a result, comparison of outcomes after various treatments is based on retrospective reviews. However, a recent study, presented by Di Stasi and colleagues during the EAU 2006 annual meeting, reported the results of an interim analysis of a multicentre, prospective randomised trial comparing radical retropubic prostatectomy with conventional EBRT in patients with clinically localised PCa ($N=137$) [9]. As shown in Fig. 3, no significant differences between EBRT and radical prostatectomy in terms of survival rates or clinical disease progression after a limited follow-up period of 67 mo could be detected. In general, patients undergoing radical prostatectomy reported a significantly worse urinary function, but better bowel function than those treated with EBRT (both $p<0.001$). Sexual dysfunction was reported more often by patients treated with radical prostatectomy compared to EBRT (70.2% vs. 61.2%, respectively), but the difference was not significant [9]. However, it should be emphasised that the main difference in induced sexual dysfunction between both therapies is probably due to the delay in sexual dysfunction following radiation therapy, which is no longer linked to the treatment. Whereas radical prostatectomy is associated with an immediate loss of sexual function, radiation therapy often results in a steady decline in sexual function over time. Longer follow-up data in a larger sample size are needed to confirm these findings.

During the ASTRO 2006 annual meeting, participants discussed the fact that the delivered radiation dose distribution is not the same as prescribed because of external and internal patient motion. Several studies were presented on adaptive radiation therapy for the treatment of PCa. The system of real-life tracing of the prostate gland with the Calypso 4D Localisation System (“Calypso system”), an investigational patient-positioning device, allows a significant improvement in dose distribution. It is based on the tracking through an external receptor of the position of three markers implanted in the prostate. Adaptive radiation therapy also provides the opportunity for therapeutic interventions to be implemented during patient radiation, as the motion of the target organ can be observed and quantified [10,11]. Apart from the “Calypso system”, other image-guiding strategies, such as cone beam computed tomography scans, were discussed [12].

The long-term toxicity outcomes of high-dose conformal EBRT (23% of patients $\leq 70.2$ Gy, 30% of patients 75.6 Gy, and 47% of patients 81 Gy) were investigated by Shippy et al in 1571 patients with T1–T3 PCa [13]. The overall grade 2 and $\geq$ grade 3 rectal toxicities at 10 yr were 8% and 1%, respectively, and 12% and 4% for urinary toxicities. The rate of severe (grade $>2$) side-effects was low.

A randomised, double-blind, placebo-controlled, crossover study assessed the efficacy of tadalafil 20 mg in 60 patients with erectile dysfunction following EBRT [14]. A significant increase in mean scores of the International Index of Erectile Function (IIEF) versus baseline was reported with tadalafil ($p<0.001$), but not with placebo. The use of tadalafil resulted in an improvement in erectile function in 67% of patients and successful intercourse in 48% of patients (Fig. 4).

Hypofractionation radiotherapy (administration of larger doses per fraction) offers the potential to enhance the therapeutic index. Martin and coworkers demonstrated that hypofractionated

![Fig. 3](image.png)

**Fig. 3** – There were no significant differences between external-beam radiation therapy (EBRT) and radical prostatectomy (RP) in terms of survival rates or clinical disease progression after a follow-up period of 67 mo [9].

![Fig. 4](image.png)

**Fig. 4** – Patients taking tadalafil showed a significant increase in mean scores of International Index of Erectile Function (improvement in erectile function and successful intercourse) versus placebo [14].
radiotherapy (60 Gy, 20 fractions during 4 wk) is feasible and associated with low rates of late bladder and rectal toxicity in patients with localised PCa [15]. Biochemical outcomes seem comparable to published conventional fractionated controls (74 Gy, 35 fractions), but longer follow-up is needed. A multicentre, phase 3 trial, comparing 60 Gy in 20 fractions with 78 Gy in 39 fractions is ongoing. For low-risk PCa, hypofractionated radiotherapy seems a feasible option considering its minimal urinary and rectal toxicity. However, in these patients its efficacy was questioned [16].

Biochemical failure based on the previous ASTRO definition (three consecutive rises of the PSA above the nadir) predicts clinical failure and cause-specific survival. However, this definition includes back-dating, which results in an artificial flattening of the Kaplan-Meier curves and overly favourable estimates when follow-up is short. Another definition, the Phoenix (or nadir +2 ng/ml) definition avoids these problems, has been associated with less misclassification following withdrawal of androgen deprivation, and has a better sensitivity and specificity for clinical failure. This was demonstrated by the study of Abramowitz and colleagues who indicated that the nadir +2 definition was a significantly more robust predictor for overall mortality, cause-specific mortality, and distant metastasis as compared to the ASTRO definition [17].

6. Hormone therapy

Hormone therapy, consisting of various forms of androgen manipulation and androgen receptor interaction, has been the primary form of systemic therapy for PCa. Because the androgen receptor is the primary driver of cell growth for PCa, reduction of androgen receptor stimulation can be accomplished by depleting the circulating androgens, blocking the binding of androgens to their receptors, or a combination of the two methods [18].

Investigators involved in the EORTC trial 30891 showed an overall survival advantage of immediate hormone therapy over deferred treatment initiated at the time of symptomatic disease progression [19] in M0 patients not suitable for a local curative treatment. During the EAU 2006 annual meeting, the authors presented the results of a subgroup analysis to evaluate which patient groups need immediate treatment. A total of 944 patients with T0–T4 N0 M0 (473 followed watchful waiting, 471 followed immediate treatment) were classed into eight subgroups based on age (≤70 yr, >70 yr) and PSA (≤8 ng/ml, 8.1–20 ng/ml, 20.1–50 ng/ml, >50 ng/ml). It was concluded that patients older than 70 yr with a baseline PSA ≤ 50 ng/ml may not benefit from immediate hormonal treatment, whereas in patients ≤70 yr, a lower PSA threshold (<20 ng/ml) must be identified to determine which patients probably benefit from immediate treatment [19].

In the same trial, the prognostic value of PSA doubling time (PSADT) as predictor of objective progression or death in a watchful waiting cohort was evaluated [20]. Patients in the watchful waiting cohort with a PSA >50 ng/ml were at a 1.5-fold increased risk of death and at a 2-fold increased risk of death due to PCa or objective progression compared to patients with initial PSA <50 ng/ml. Only 11% of patients with PSA <8 ng/ml died from PCa. In a subgroup of 140 patients with PSA levels between 8 and 50 ng/ml and a minimum of 1 yr follow-up with PSA tests, patients with an estimated PSADT <12 mo had a 3-fold increased risk of death (p < 0.001), a 5-fold increased risk of death due to PCa (p < 0.001) and a 4-fold increased risk of objective progression (p < 0.001) compared to those with a longer PSADT. It was therefore concluded that patients with a PSA between 8 and 50 ng/ml and a PSADT <12 mo are at high risk of disease progression and subsequent death due to PCa and should therefore be considered for immediate hormone therapy [20]. During the closed meeting it was highlighted that currently also the PSA-V (rather than the PSADT) has become an important criterion for determining those patients with PCa who are at risk of disease progression. It was mentioned that a 20% biologic variation of PSA exists in patients without having variation in the disease status [21]. When asking the audience how they deal with the risk of PCa progression, the majority indicated that they focus on PSA-V rather than PSA thresholds.

There is a growing interest for intermittent hormone therapy because of its potential for an improved side-effect profile compared to continuous hormonal treatment. During the ASCO 2006 annual meeting, Calais Da Silva and colleagues presented the outcomes of their randomised, controlled trial comparing continuous and intermittent hormone therapy [22]. Patients (N = 626) with locally advanced or metastatic PCa (T3–T4 or M+) were randomised to intermittent hormone therapy (N = 314) or continuous therapy (N = 312) after an initial induction treatment of 3 mo with cipotereone acetate 200 mg plus injections of luteinising hormone-releasing hormone (LHRH) analogues and a decrease in PSA <4 ng/ml or to below 80% of the initial value. The estimated 5-yr survival was 53.8%
in the intermittent group and 51.0% in the continuous group. The main difference in quality of life between the two arms of the study was related to sexual function. Sexual activity was significantly greater ($p < 0.01$) in the patients in the intermittent arm. In this group, 41% of men reported sexual activity at 9 mo, 40% at 15 mo, and 35% at 21 mo. The most commonly reported side-effects were hot flushes, which appeared more frequently in the patients in the continuous arm than in those in the intermittent arm (30% vs. 20%, respectively, $p < 0.01$). There was no evidence that intermittent therapy led to a significantly elevated hazard of dying ($p = 0.79$) or to a greater subjective or objective progression ($p = 0.52$) [22]. These results support the use of intermittent therapy in clinical practice. More studies are ongoing to evaluate the true benefits of intermittent therapy in men with advanced PCa. If the approach proves to be as effective as continuous therapy in suppressing tumour growth, intermittent therapy will likely become popular because it has less impact on the patient’s quality of life.

When raising the question to the audience which hormonal treatment regimen they used, the majority indicated to use intermittent hormone therapy, which is in line with the results of the study by Calais Da Silva [22]. It should, however, be noted that this study deals with patients with advanced PCa, for whom surgical treatment is no longer an option. During the discussion the point was made that one should be very careful when addressing intermittent hormone therapy. Investigators should consider the difference between clinical and biochemical intermittent hormone therapy. It is not because physicians are clinically administering hormones intermittently that the castration is really intermittent and not continuous [23,24]. It is therefore of critical importance not only to measure PSA but also to measure the testosterone level of the patient during hormone treatment. The general consensus is that testosterone is the target of hormone therapy, but only recently have tools become available to accurately determine testosterone levels. During the discussion, the general remark was made that physicians should shift from a PSA-obsessed era and should also take testosterone levels into account.

7. Metastatic PCa

Advanced cancers frequently metastasise to the bone, resulting in bone destruction that is associated with a variety of skeletal complications. Estimates indicate that worldwide 1.5 million patients with cancer have bone metastases. In addition to standard anticancer therapy, treatment options for bone metastasis include radiation therapy, surgery, bisphosphonates, and analgesics [25]. In normal healthy bone there is a steady-state balance between osteoblastic bone formation and osteoclastic bone resorption, which is lost when tumour cells enter the bone microenvironment. Bisphosphonates directly affect osteoclasts. However, some evidence indicates that bisphosphonates are able to directly affect tumour cells by inducing apoptosis of tumour cells and inhibition of tumour cell growth in vitro [26].

Treatment with LHRH agonists decreases bone mineral density (BMD) and therefore increases the risk of bone fractures in men with PCa. Michaelson and colleagues compared the effects of zoledronic acid (ZA) with placebo in patients with nonmetastatic PCa [27]. The results were presented during the annual ASCO 2006 meeting. It was shown that patients receiving a single administration of ZA presented with a mean ± standard deviation increase in lumbar spinal BMD of $4.0 \pm 0.9$, which was significantly different from patients receiving placebo at 1 yr after injection (mean decrease $3.1 \pm 0.9; p < 0.001$; Fig. 5) [27]. It was concluded that a single annual injection of ZA might provide a convenient and effective strategy to prevent bone loss in men with nonmetastatic disease receiving hormone therapy. Another study presented by Saad and colleagues at the EAU investigated whether ZA maintains efficacy after the occurrence of a previous skeletal-related event. It was concluded that ZA offers ongoing benefit to men with PCa and bone metastasis even after a previous bone-related event [28].

During the discussion at the closed meeting it was highlighted that one injection of ZA yearly may prevent bone loss in patients on androgen-deprivation therapy and could therefore be considered at

![Fig. 5](https://example.com/fig5.png)

Fig. 5 – In patients receiving a single administration of zoledronic acid (ZA) lumbar spinal bone mineral density (BMD) was significantly increased compared to patients receiving placebo ($p < 0.001$) [27].
the time of hormonal treatment induction. Furthermore, it was discussed that the significance of bone fractures is probably strongly underestimated. A phase 3, double-blind, placebo-controlled study (RTOG 0518) has recently been launched by the Radiation Therapy Oncology Group to evaluate the efficacy of ZA for the prevention of osteoporosis and associated fractures in patients receiving radiation therapy and long-term LHRH agonists for high-grade or locally advanced PCa.

8. Chemotherapy

For patients with hormone-refractory advanced PCa (HRPC), first-line chemotherapy with docetaxel is becoming a standard treatment. Accumulating evidence in clinical trials has shown that the combination of docetaxel with estramustine may have a synergistic effect [29]. However, the potential of combining docetaxel with estramustine still remains to be determined in clinical practice [29]. Estramustine is associated with specific side-effects and randomised phase 3 trials comparing docetaxel with or without estramustine are currently lacking. In a phase 2 trial, Caffo et al evaluated the efficacy of docetaxel plus estramustine in terms of PSA decline and tolerability in HRPC patients (ie, those patients who present with PSA progression after at least two hormonal therapies) [30]. As shown in Fig. 6, more patients receiving the combination of docetaxel and estramustine have a PSA decrease ≥50% and PSA normalisation compared to docetaxel alone. Both treatment regimens were well tolerated. Based on these preliminary data, the authors concluded that in HRPC patients docetaxel-based regimens are effective with a low toxicity profile [30]. However, more prospective trials are needed to evaluate the benefit of adding estramustine to docetaxel, because the survival rate in this study was comparable to that from two other trials in which patients received docetaxel on a 3-weekly schedule or the combination of docetaxel and estramustine [31,32].

During the closed meeting, it was noted that estramustine is rarely used in clinical practice because of the side-effects that patients experience with the high doses used.

9. Conclusions

The major urologic congresses in 2006 provided many interesting data on the surveillance and treatment of patients with PCa. Much of the discussion was related to the relevance of PSA screening. There seems to be no PSA threshold level for early detection of clinically significant PCa. PSADT and PSA-V may provide physicians with a more detailed picture of the patient and may be more reliable to predict the risk of PCa progression. Patients with an initial PSA of 8–50 ng/ml and a PSADT <12 mo seem to be at high risk for progression and death due to PCa and probably need immediate hormone therapy.

The first randomised controlled trial comparing radical prostatectomy with EBRT showed no significant differences between the treatments in terms of survival or disease progression, but caution is warranted when comparing the side-effects of both treatment options, except if they are based on self-administered questionnaires. Of course, more direct comparative, long-term studies are needed before definitive conclusions can be drawn regarding the efficacy and safety of various surgical treatments for PCa. Furthermore, not every treatment is suitable for each patient, and patient preferences will also influence the final treatment selection.

There is currently a trend to administer hormone therapy intermittently because this has less impact on the patient’s quality of life than continuous hormonal administration. Data from a direct comparative trial demonstrated that intermittent therapy is comparable to continuous hormone therapy with regard to estimated survival at 5 yr, disease progression, and death due to PCa. To prevent the risk of bone complications in patients with PCa receiving hormone therapy, one yearly injection of ZA could be of interest.
Finally, combination chemotherapy with docetaxel and estramustine may improve survival rates in HRPC patients, but phase 3 trials are needed.

References


