1. **Introduction**

Global cancer incidence rates show that prostate cancer (PCA), with more than 670,000 new diagnoses each year, has become the second most common cancer in men after lung cancer [1]. The highest incidence rates are found in industrial countries, whereas China and India have the lowest incidence rates. Despite this obvious discrepancy between countries, substantial increases in incidence have
been reported in recent years for many countries around the world [2]. Although this increase has been suggested to result from the improved detection of PCa following transurethral resection of the prostate (TURP) and, more recently, from the advanced screening method based on detection of prostate-specific antigen (PSA), longer life expectancy and increased disease prevalence resulting from environmental carcinogens may also contribute to the increased incidence [3]. Whether or not the observed increase is “real,” the number of cases is expected to keep on rising as the population at risk (older men) expands because of increasing life expectancy.

In recent years, stage distribution data have shown that 91% of men are diagnosed with PCa while the cancer is still confined to the primary site or after the cancer has spread to regional lymph nodes (localised or regional PCa), while only 5% are diagnosed after the cancer has metastasized (distant stage). In the latter case, the 5-yr survival is only 33.3%, whereas patients diagnosed with localised or regional PCa have a 5-yr survival rate of 100% (www.seer.cancer.gov). These substantial differences in survival rate emphasise the importance of early detection of PCa and the ongoing necessity to optimise and further improve the management of PCa.

Recent developments in the detection and management of PCa were presented in 2006 at the annual meetings from the European Association of Urology (EAU), the American Urological Association (AUA), and the American Society of Clinical Oncology (ASCO). A selection of interesting studies in PCa presented at these congresses was discussed during the “New Horizons in Urology” meeting in Marbella, Spain. Furthermore, participants to this meeting were asked to express their opinion on representative clinical case studies, illustrative of the chosen studies, by means of interactive voting. The results from this voting procedure were commented on by experts in the field of PCa.

2. Screening and detection

The introduction of PSA as a screening tool has profoundly altered the aspects of PCa detection in the past few decades. Although no universal PSA threshold is accepted, a PSA level >4 ng/ml is nowadays widely used as predictive for the diagnosis of PCa [4]. Over the past few years, however, there has been discussion on whether to lower the threshold because of data indicating that a significant amount of PCa can be detected in men with PSA < 4 ng/ml [5]. In light of the increase in the number of biopsies and the increased detection of insignificant PCa associated with the reduction of the PSA cut-off value [4], the debate is still in progress on whether low PSA values truly correlate with an increased risk for PCa. At the EAU 2006 annual meeting, results were presented on a retrospective study investigating the diagnostic yield of two PSA cut-off values, 2.5 ng/ml and 4.0 ng/ml [6]. Between January 1999 and December 2004, a total of 555 men underwent a routine 8-core biopsy as a result of a suspicious digital rectal examination (DRE) or a PSA level >2.5 ng/ml. Of these men, 263 had a PSA < 4 ng/ml, whereas in 292 patients a PSA level between 4 and 10 ng/ml was detected. PCa was detected in 24.1% of the patients, of whom a significantly higher percentage had a PSA between 4 and 10 ng/ml (Fig. 1; \(p < 0.001\)). Furthermore, it was demonstrated that PCa detected in patients with PSA < 4 ng/ml had a more favourable pathologic outcome upon biopsy (Gleason score \( \geq 7 \)) compared with PCa specimens from patients with PSA between 4 and 10 ng/ml (Fig. 1; \(p = 0.09\)). In light of these results, it was concluded that there is no distinct PSA threshold suitable for the early detection of clinically relevant PCa [6]. This conclusion corresponded to that of the experts at the closed meeting in Marbella, who, once again, stated that it is difficult to rely on a PSA cut-off value of 4 ng/ml for real screening procedures.

3. Natural history

Active surveillance or watchful waiting is a treatment strategy especially for men with favourable
tumour characteristics and includes an active standpoint to postpone treatment until evidence of disease progression [4]. At the AUA 2006 annual meeting, a study was presented that evaluated the clinical profiles and outcomes of men with PCa who were initially managed with active surveillance [7]. A total of 240 patients were selected for active surveillance, of whom 140 met all of the following inclusion criteria: PSA < 10 ng/ml, Gleason score ≤ 6 (with no pattern 4 or 5), cancer involvement of <33% of biopsy scores, and clinical stage T1–T2a. Patients were monitored by PSA measurements and DRE examination every 3–6 mo, transrectal ultrasound (TRUS) at 6- to 12-mo intervals, and repeat biopsy at 12–24 mo. Overall, patients had a mean follow-up of 2.6 yr. A total of 152 men underwent repeat biopsy, and 27% of them had evidence of disease progression at a mean time of 3.6 yr. The overall risk for disease progression at 5 yr was <10% for patients who met all the inclusion criteria, whereas this risk was substantially higher for those patients who did not meet all the criteria (Fig. 2). Although there was no evidence of disease progression, 4% of the patients chose definitive treatment at a mean time of 1.5 yr after initiating active surveillance. It was concluded that active surveillance of PCa is possible if patients are carefully selected with the use of specific criteria. Nevertheless, it was suggested that further follow-up in a larger number of patients is needed to further validate this kind of treatment strategy [7].

Besides providing a good basis for active surveillance, monitoring PSA values over time may also form the basis to calculate the PSA doubling time (PSADT). This tool is mainly used to predict outcomes such as time to progression and PCa-specific mortality [8]. At the EAU 2006 annual meeting, Collette and colleagues [9] assessed the prognostic value of PSADT as predictor of objective progression or death. One hundred forty eligible patients retrieved from the watchful waiting arm of the European Organisation for Research and Treatment of Cancer (EORTC) trial 30891 were assigned to this study because they had a baseline PSA value between 8 and 50 ng/ml, and a minimum of 1-yr follow-up. Patients had a median of three follow-up PSA measures with a median interval of 187 d. A total of 67 patients died, 23 (16.4%) from PCa. It was shown that patients with an estimated PSADT < 12 mo were at an approximately 5-fold increased risk for death due to PCa (p < 0.001) and at a 4-fold increased risk of objective progression (p < 0.001) compared with patients with longer PSADT. It was concluded that PSADT of <12 mo should be regarded as an important threshold associated with a high risk for progression and death due to PCa.

4. Histopathology

The role of the pathologist has proven essential, not only in diagnosing PCa but also in planning therapeutic and management strategies [10]. Pathologic data depend on an individual’s interpretation of histologic source material and therefore should be treated with caution. With respect to this issue, van der Kwast and colleagues [11] presented data on their critical pathologic review of prostatectomy specimens. This study was part of the EORTC trial 22911 in which 503 patients previously treated with radical prostatectomy (RP) were randomly assigned to the control arm and 502 patients to immediate postoperative radiotherapy. A total of 552 prostatectomy specimens (280 control arm, 272 test arm) obtained in 12 major centres were reviewed by a single pathologist for stage, margin status, and Gleason score. Results demonstrated that there was a high agreement between local pathologists and the review pathologist with regard to seminal vesicle involvement (κ = 0.83), but this agreement was low for extracapsular extension (κ = 0.33) and margin status (κ = 0.45). The overall agreement for extracapsular extension and margin status was 57.5% and 69.4%, respectively. From this finding it was concluded that there was a marked discrepancy between local pathologists and the review pathologist on the histopathologic evaluation of prostatectomy specimens with regard to extracapsular extension and margin status, whereas a higher agreement was seen on seminal vesicle involvement.
Hence, it was emphasised at the closed meeting in Marbella that pathology results are a piece of information within a global set of parameters that should all be taken into account before a decision is made regarding therapy.

5. Predictive value of Partin tables

Partin tables were developed to estimate the pathologic stage of PCa on the basis of PSA level, Gleason score, and clinical stage; they have become an important tool in guiding decisions about effective treatment of PCa [12,13]. A study presented at the EAU 2006 annual meeting evaluated the predictive value of the Partin tables in assessing the risk of lymph node involvement in patients undergoing RP for clinically localised PCa [14]. Seven hundred forty-eight patients with cT1c PCa, a preoperative PSA < 10 ng/ml, and a biopsy Gleason score ≥ 6 underwent RP with extended pelvic lymphadenectomy. Lymphatic tissue was examined histopathologically and postoperative data were correlated with the calculated risk of lymph node involvement as predicted by the Partin tables. A median of 20 (range 1–72) lymph nodes were removed per patient. Overall, 44 patients (5.6%) were diagnosed with pelvic lymph node metastases, with 19 patients having one positive lymph node, and 15 and 10 patients exhibiting two and two or more positive lymph nodes, respectively. A preoperative biopsy Gleason score of 2–4 and 5–6 was found in 75 (13%) and 494 (87%) of the patients, respectively. In 4 of 75 (5.3%) and in 40 of 494 (8.1%) of these patients, positive lymph nodes were identified (Fig. 3). However, the predicted risk for lymph node involvement according to the Partin tables was 0% and 2% for Gleason scores 2–4 and 5–6, respectively (Fig. 3). Therefore, it was concluded that Partin tables are not suited for the prediction of lymph node involvement in patients with clinically localised PCa [14]. Overall, Partin tables remain an important tool for urologists, oncologists, and surgeons, but one should keep in mind that these tables are not 100% reliable.

6. Treatment of localised disease

6.1. Laparoscopic radical prostatectomy

In the past several years, laparoscopic RP (LRP) has become an accepted alternative to open surgery. For both open and LRP, the presence of positive surgical margins (PSMs) is associated with an increased risk for biochemical and local recurrence [15]. It has been shown that a PSM ≤ 1 mm in size on intraoperative frozen section of the posterolateral surface correlates with negative margins on subsequent permanent sections [16]. At the AUA 2006 annual meeting, the impact of these PSMs ≤ 1 mm on intermediate outcomes after LRP was evaluated [17]. Of 2600 patients who underwent LRP between 1998 and 2005, 330 patients had a 5-yr follow-up and were included in the study. Overall, 60 patients had PSMs, of whom 27% had a margin size ≤ 1 mm, 28% had margins > 1 mm but ≤ 3 mm, and 45% had a margin size > 3 mm (Fig. 4). Biochemical recurrence at 5 yr of follow-up was seen in 5.0%, 8.3%, and 16.7% of the patients belonging to these respective groups (Fig. 4). Patients with PSMs ≤ 1 mm had significantly greater biochemical disease-free survival (BDFS) compared...
with those from the other two groups ($p < 0.02$); however, there was no significant difference in BDFS between patients with PSM $\leq 1$ mm and those with an overall negative margin status. It was concluded that, on the basis of their BDFS, patients with PSM $\leq 1$ mm after LRP have intermediate outcomes comparable to those of patients who have a negative margin status after surgery. However, it should be kept in mind that 18.7% of the patients with a PSM $\leq 1$ mm still had signs of biochemical progression at 5 yr of follow-up [17].

6.2. Radiation therapy

Radiation therapy, comprising external beam radiation therapy (EBRT), brachytherapy, or a combination of both, is an established treatment strategy for patients with localised or locally advanced PCa. Still, there are no randomised studies available comparing either of these radiation treatment options with RP [4]. At the EAU 2006 annual meeting, however, results were presented on the first multicentre, prospective, randomised trial comparing EBRT with retropubic RP by Di Stasi and colleagues [18]. Between January 1997 and September 2001, 137 patients with clinically localised newly diagnosed PCa were randomised to either RP ($N = 70$) or EBRT ($N = 67$), and data gathered during follow-up consisted of evidence of clinical disease progression, survival rates, and information on disease-specific health-related quality of life (QoL). After a median follow-up of 67 mo (range: 24–88), interim analysis results indicated that there were no significant differences between EBRT and RP in terms of clinical disease progression and survival rates (Fig. 5). However, patients who underwent RP experienced a significant decrease in their health-related QoL ($p < 0.001$) the first month after treatment compared with EBRT. Both groups, however, showed a decline in their sexual function throughout the posttreatment period (Fig. 5). These results indicate that there are no major differences in outcomes between RP and EBRT, but a follow-up period of 67 mo is too short to draw definitive conclusions. The suggestion was made that confirmation is warranted with an additional larger sample size and a longer follow-up period [18].

In recent years, brachytherapy has become an accepted and standard means of therapy and is now an important therapeutic option available to radiation oncologists and urologists worldwide [19]. At the AUA 2006 annual meeting, the long-term biochemical (PSA) freedom from failure (bFFF) of brachytherapy was investigated in 1562 men diagnosed with T1–3 PCa [20]. Between 1990 and 2002, 54.7% of the patients were treated with radioactive iodine ($^{125}$I), whereas 12.5% and 32.8% were treated with palladium ($^{103}$Pd) or $^{103}$Pd combined with EBRT, respectively. Of these patients, 43.2% were regarded as low-risk patients, whereas 25.1% and 31.7% were categorised into intermediate- and high-risk patients, respectively. The median follow-up of the study was 5 yr (range: 2–15). The bFFF rate of the entire cohort was 84% at 12 yr with 88%, 90%, and 73% in low-, intermediate, and high-risk patients, respectively. Furthermore, $^{125}$I, $^{103}$Pd, or the combination therapy was associated with a bFFF rate of 86%, 75%, and 87% respectively. From these results, it was concluded that brachytherapy results in a low-level biochemical recurrence if patients are carefully selected [20].

6.3. High-intensity focused ultrasound (HIFU) as alternative treatment strategy

HIFU involves the emission of focused ultrasound waves inducing tissue damage by the conversion of mechanical energy into heat and by cavitation [21]. Although HIFU is a technique that is not associated with the invasive character of surgical intervention, patients treated with HIFU are likely to experience significant posttreatment discomfort attributable to HIFU-related side-effects [4]. At the EAU 2006 annual meeting, Thueroff and colleagues [22] analysed the side-effects resulting from >1300 HIFUs that were performed in a prospective single cohort study in men with localised PCa between April 1996 and November 2005. During follow-up, side-effects were documented and categorised into five main groups: systemic, micturition, infection, sexual, and rectum/pelvis problems. A total of 2745 events were
registered, of which 42% were judged to be “therapy related”; the most frequent ones are summarised in Table 1. These results indicate that HIFU is associated with low morbidity; however, side-effects tend to increase with the number of local pretreatments.

## 7. Treatment of advanced disease

### 7.1. Hormonal therapy

Hormonal therapy aims at depriving androgens, either through the suppression of androgen secretion by means of surgical or medical castration or through inhibition of the action of circulating androgens by using antiandrogens. Alternatively, these two approaches can be combined to achieve maximal androgen blockade (MAB). Although MAB has been proven to result in a small advantage in overall survival compared with castration alone, it is associated with increased adverse events and reduced QoL [4]. In this respect, intermittent hormonal therapy might be a good alternative because of its potential to preserve the patient’s QoL during the off-therapy periods. A randomised, phase 3 study [23] presented at the ASCO 2006 annual meeting compared intermittent versus continuous hormonal therapy. After an initial induction period of 3 mo with 200 mg cyproterone acetate and injections with luteinising hormone-releasing hormone (LHRH) analogue, and a PSA decrease below 4 ng/ml or to 80% of their initial value, 626 patients with locally advanced or metastatic PCa were randomised to intermittent hormonal therapy (N = 314) or continuous therapy (N = 312). The estimated 5-yr survival was 53.8% in the intermittent group and 51.0% in the continuous group. Furthermore, it was demonstrated that intermittent therapy does not lead to an elevated hazard of dying (p = 0.79) or to a greater objective or subjective progression (p = 0.52) compared with continuous therapy. The main differences in QoL were confined to sexual function: Sexual activity was greater in the intermittent arm with 41%, 40%, and 35% of men reporting sexual activity at 9, 15, and 21 mo, respectively. The most commonly reported adverse events were hot flushes, which were significantly more prominent in the continuous arm (30%) than in the intermittent arm (20%, p < 0.01). Together, these results support the use of intermittent hormonal therapy in clinical practice because it is comparable to its continuous counterpart on the basis of disease control, but with a clear advantage for the patient’s sexual function. However, more evidence should be provided to confirm that both modalities are equally effective.

### 7.2. Bone complications

Although androgen-deprivation therapy (ADT) is an effective treatment strategy for patients with PCa, it is associated with accelerated bone loss, osteoporosis, and an increased risk for fractures, even in patients without bone metastases [24]. At the EAU 2006 annual meeting, Casey and colleagues [24] presented results from an open-label, controlled, multi-centre study that investigated whether zoledronic acid (ZA), known to be effective against skeletal complications in patients with bone metastases, can prevent bone loss in PCa patients without bone metastases on ADT therapy. Over a 12-mo period, 200 hormone-naïve men with locally advanced PCa were randomised at a 1:1 ratio to a control group receiving goserelin acetate alone or to a treatment group receiving ZA (4 mg every 3 mo for 1 yr) and goserelin. At 12 mo, the interim results of 80 patients demonstrated that the mean bone mineral density (BMD) at all sites (lumbar spine, femoral neck, and hip) decreased from baseline in the control group. In contrast, mean BMD in the treatment group increased at all sites, and the overall differences in BMD between both groups were shown to be significant at all sites (p = 0.0005, p < 0.0001, and p = 0.0012 respectively). In addition,

### Table 1 – Most frequent side-effects associated with high-intensity focused ultrasound [22]

<table>
<thead>
<tr>
<th>Side-effects Primary HIFU mono</th>
<th>Second HIFU</th>
<th>HIFU salvage after multiple local pretreatments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (N)</td>
<td>1078</td>
<td>156</td>
</tr>
<tr>
<td>Catheter time (median days)</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Erectile dysfunction (%)</td>
<td>55</td>
<td>75</td>
</tr>
<tr>
<td>Urinary tract infection (%)</td>
<td>9.5</td>
<td>15.3</td>
</tr>
<tr>
<td>Stress incontinence (&gt;3 mo) (%)</td>
<td>1.7</td>
<td>2.2</td>
</tr>
<tr>
<td>TURP after (%)</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Rectourethral fistula (after 1999) (N)</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

HIFU = high-intensity focused ultrasound; TURP = transurethral resection of the prostate.
it was shown that the combination of ZA and goserelin had an acceptable safety profile with mild to moderate adverse events. It was concluded that ZA is effective and well tolerated for the treatment and prevention of bone loss in men undergoing ADT with an LHRH analogue.

8. Case studies

During the closed expert meeting “New Horizons in Urology,” held October 2006 in Marbella, the opinion of the participants with respect to two representative cases regarding PCa was assessed by an interactive voting procedure. The results were discussed and commented on by experts in the field of PCa.

8.1. Case 1

A 68-year-old man without lower urinary tract symptoms (LUTS) went to his general practitioner for his checkup. He had a PSA value of 8.2 ng/ml with a free/total PSA ratio of 0.09. Upon DRE, a clear hard nodule was found on the left apical side, which, clinically, could already be considered a T3 lesion. A TRUS was made and showed a hypoecho on the left apex, thereby confirming the DRE impression. Afterwards, the patient had biopsies and 8 of 12 were positive, for a Gleason 4 + 3.

With this information in mind, the first question posed to the audience was what the risk for biologic progression at 5 yr would be for this patient after curative treatment. The participants were asked to choose from three options. Sixty-five percent of the participants thought that the risk for progression at 5 yr was between 30% to 40%, whereas 27% believed the risk to be 60% to 70% and only 8% thought that the risk was <10%. The experts commented that the majority of the attendees were on the right track because the risk is usually between 40% to 50%.

Next, the participants were asked to choose from six possible treatment options if the patient was N0 M0. The majority choose RP (43%), one third went for EBRT plus LHRH agonist, whereas the reminder was divided between the other four options (Fig. 6). Although the majority choose RP, the patient eventually received radiation therapy combined with LHRH agonists for 3 yr. The experts commented that, because of the age of the patient and the therewith associated probability of his being unfit for surgery, normally one should not opt for RP. However, in recent years the elderly tend to be more fit at advanced age, so that, if carefully selected, these patients could be candidates for RP. It was, however, mentioned by the experts that, in this case, RP alone would probably not be sufficient and should be combined with either radiation or hormonal therapy.

Five years after ending LHRH agonist therapy, a PSA increase was measured: 3.9 to 5.1 to 6.4 ng/ml in 1 yr. Again, the attendees were asked to choose a treatment strategy. The majority opted for LHRH agonist treatment again (53%) and 31% went for ADT, whereas the minority was divided between HIFU (7%), salvage prostatectomy (5%), salvage brachytherapy (2%), and salvage chemotherapy (2%). In line with the majority, the patient got LHRH agonist treatment again. Although the experts overall agreed with this treatment strategy, they remarked that perhaps one should wait longer before initiating further treatment, considering the fact that it took 5 yr before the patient’s PSA started rising.

8.2. Case 2

The second case was a 66-year-old man with severe LUTS. He had an international prostate symptom score (IPSS) of 24 and a PSA of 3.2 ng/ml. DRE examination did not show irregularities. He was initially put on α1-adrenoceptor antagonists, but after failure he underwent TURP. After histopathologic analysis of the TURP specimens, PCa was found with Gleason 2 + 3 and only 3% of the chips showed very focal disease (T1a).

Assessment of the treatment preferences of the participants showed that 65% chose active surveillance, 29% opted for prostatectomy, and HIFU and
LHRH agonist each got 3% of the votes. In line with the majority, the patient was actively followed with PSA measurement and DRE every 6 mo. During follow-up, PSA progressed from 1.2 ng/ml post-TURP to 1.6, 2.1, and 2.7 ng/ml at 6, 12, and 18 mo, respectively. Prostate biopsies were done again and only 2 of 12 cores were positive. They all had the same grade: Gleason was 2 + 3 and limited to only 10–20% of the core length on the right side. Again, the participants’ preferred treatment strategy was assessed by interactive voting. Approximately half of the attendees chose RP, a quarter of them would continue active surveillance, and 15% would go for radiation therapy, whereas only few participants chose LHRH agonists, HIFU, or brachytherapy (Fig. 7). The patient was treated with RP, although this treatment option was doubted afterwards by the treating expert. It was suggested that more TURP probably would have cured the patient. Although a reasonable part of the attendees chose radiation therapy, the experts commented that this approach certainly is not a favourable option after TURP.

9. Conclusions

Research on PCa produced numerous new interesting data that were presented at the 2006 key urologic and oncologic meetings. Although there has been a lot of debate on lowering the PSA threshold below 4 ng/ml, it was shown that there is no distinct PSA threshold for the early detection of PCa. However, PSA remains an important tool, not only for initial diagnosis but also for active surveillance of patients. In this respect, it was demonstrated that active surveillance of PCa is feasible provided that patients are carefully selected. An important aid in this active surveillance is the interpretation of the PSADT. It was concluded that a PSADT < 12 mo should be considered an important threshold because it is associated with an increased risk of progression and death due to PCa. In addition, it was shown that pathology results and Partin table predictions are not always 100% reliable. They should be regarded as important pieces of information within a global set of parameters, which should all be considered before making a decision about a suitable treatment strategy.

RP is still the favoured therapy for patients with localised disease. Although laparoscopic surgery is beneficial for the patient’s QoL, it is also associated with an increased risk of PSM. It was, however, shown that patients with a PSM ≤ 1 mm after LRP have comparable intermediate outcomes compared with patients with a negative margin status after surgery. Clearly, however, these results should be verified in a long-term follow-up setting. In addition, treatment of localised disease with radiation therapy was found to be comparable to RP concerning survival and disease progression. HIFU is associated with low morbidity, but also increased side-effects if the number of local pretreatments rose.

With regard to advanced disease, it was demonstrated that intermittent hormonal therapy might be an option for clinical practice because it is comparable to continuous hormonal therapy in terms of disease control, but is associated with an improved sexual function. However, this seemingly equal effectiveness of both modalities should be further confirmed in a larger-scale study with a longer follow-up period. Finally, it was found that zoledronic acid is able to prevent bone complications in patients on ADT and, therefore, should perhaps be considered a standard supplementary agent during ADT.

Conflicts of interests

The author has nothing to disclose.

References