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Biomarkers of Aggressiveness in Prostate Cancer

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1. Introduction

Although significant progress in the investigation of prostate cancer biomarkers, some men are overdiagnosed with indolent prostate cancer while others die from aggressive disease diagnosed too late. The introduction of PSA (Prostate Specific Antigen) in clinical practice has resulted in early detection and reduced mortality from prostate cancer (Schroder et al., 2009). Despite its great utility for prostate cancer detection and prognostication, PSA as a single test has several limitations. Prostate cancer screening remains thus controversial, because of the risk of overdiagnosis reduced mortality and overtreatment and the inability to detect a significant proportion of aggressive tumors. To extend the limited information provided by PSA testing, other biomarkers that could discriminate between indolent from aggressive cancers are therefore an absolute must. Despite numerous studies of biomarker candidates have been presented the last decade, the identification of the most aggressive subsets of this disease is still not possible. This review will cover last years development in this area and highlight the most promising biomarkers in prostate cancer, which have been divided into three groups; protein-based, DNA-based and RNA-based markers.

2. Protein biomarkers

2.1 Prostate Stem Cell Antigen (PSCA)

PSCA (Prostate Stem Cell Antigen) is a membrane glycoprotein with 30% homology to stem cell antigen type 2 (SCA-2), an immature lymphocyte cell surface marker. Like SCA-2, PSCA is attached to the membrane by a GPI anchor which can be cleaved by a phospholipase. Because of its homology with SCA-2, PSCA was named inaccurately since it is not a marker for stem cells nor is it uniquely expressed in the prostate (Saeki et al., 2010). Initially, PSCA was identified as a tumor antigen overexpressed in the prostate (Reiter et al., 1998), and subsequent studies have revealed that it is also up-regulated in other cancers including bladder and pancreas. PSCA has been proposed as a promising tumor marker of diagnostic and prognosis, as well as a potential therapeutic target for patients with metastatic prostate cancer. PSCA expression indeed increases with high gleason score, advanced stage and bone metastasis (Gu et al., 2000; Han et al., 2004; Lam et al., 2005; Zhigang & Wenlv, 2004). The levels of PSCA are also amplified in the prostate intraepithelial neoplasia (PIN) lesions that

subsequently progressed to cancer compared to those that did not progress (Zhigang & Wenlu, 2007). PSCA might also represent a useful marker for metastasis detection as almost 95% of lymph nodes and bone samples with metastasis have been found positive for PSCA expression (Ananias et al., 2009). It was originally observed that PSCA mRNA bearing cells circulating in peripheral blood were identified at higher rates in prostate cancer patients with extraprostatic disease (Hara et al., 2002). The presence of PSCA transcripts in the peripheral blood has found to be a significant predictor of biochemical recurrence after prostatectomy in high-risk prostate cancer (Joung et al., 2010). Of note, PSCA has also been investigated as a potential target for tumor-targeted immunotherapy and for suppression by anti-PSCA antibody in animals. Further evaluation of PSCA as a clinical prostate cancer marker of aggressiveness needs to be validated.

2.2 Prostate Secretory Protein 94 (PSP94)

The ELISA dosage of β -microseminoprotein (MSP) ou PSP94 (Prostate Secretory Protein of 94 amino acids) – one of three predominant proteins secreted by the human prostate gland (Lilja & Abrahamsson, 1988) – could be potentially interesting. In a case-control study of 1,212 men with no previous history of prostate cancer, Nam et al. found that patients with low PSP94 levels had a high probability for having prostate cancer diagnosed at biopsy (Nam et al., 2006). The authors also suggested that those cancers that maintain PSP94 expression tend to be well differentiated and less aggressive, as reported in previous immunohistochemistry studies (Abrahamsson et al., 1988). In serum, PSP94 can be complexed with PSPBP (PSP-binding protein), a glycoprotein of 50 kDa sharing significant identity with the CRISP (cystein-rich secretory protein) family of proteins (Reeves et al., 2005). In a study comprising 185 patients, it was showed that PSPBP is negatively associated with recurrence after radical prostatectomy (Reeves et al., 2006). On the contrary, PSP94 immunohistochemistry performed on 59 radical prostatectomy specimens was associated with worsened survival outcomes (Girvan et al., 2005). Another immunohistochemistry study conducted on 945 patients found a high expression of PSP94 in tumor cells patients to be associated with a longer time to postprostatectomy biochemical recurrence (Bjartell et al., 2007) in agreement with serum studies. Further studies will be needed to determine whether PSP94 and its binding protein represent novel prognostic factors in the clinic.

However, it is interesting to note that genome-wide association studies identified several SNPs in a region on chromosome 10 that harbors the *PSP94* gene (Eeles et al., 2008; Thomas et al., 2008). Its location and the strength of the association raises the possibility that this SNP may be causally related to disease risk, but resequencing and further analyses will be needed clarify the functional basis of this association.

2.3 Early Prostate Cancer Antigens ECPA and ECPA-2

ECPA and ECPA-2 (Early Prostate Cancer Antigens) are nuclear matrix proteins those alterations are commonly associated with prostate cancer (Getzenberg et al., 1991; Lakshmanan et al., 1998). Initially, immunohistochemical studies on men with negative biopsies who were ultimately found to have prostate cancer could identify individuals as much as 5 years earlier than the current diagnostic (Dhir et al., 2004). ECPA positivity was hypothesized to be an early event in disease progression, as there was no correlation between ECPA staining and Gleason grade or pT stage (Uetsuki et al., 2005). In 2005, an ECPA-based ELISA showed 92% sensitivity and 94% specificity in prostate cancer detection

in patients undergoing radical prostatectomy, however only 46 blood samples were examined (Paul et al., 2005). ELISA used for initial serum EPCA measurement in 112 men with isolated high-grade prostatic intraepithelial neoplasia (HGPIN), showed a significantly higher serum EPCA level in isolated HGPIN patients with subsequent cancer than those without cancer (Zhao & Zeng, 2010). Pretreatment serum EPCA levels were also determined with an ELISA in 77 patients with clinically localized prostate cancer who underwent radical prostatectomy and 51 patients with locally advanced or metastatic disease who received primary androgen deprivation therapy, and were correlated with clinicopathological variables and disease progression. Patients with locally advanced and metastatic prostate cancer had significantly higher serum EPCA level than those with clinically localized disease. These data suggest that EPCA level correlates significantly with the poor prognosis, showing prediction potential for prostate cancer progression (Zhao et al., 2011). Unrelated to the original EPCA, the nuclear protein ECPA-2 was recently described (Leman et al., 2007). Carried out on 385 blood samples, the ECPA-2 ELISA was able to differentiate between men with and without prostate cancer with 92% specificity and 94% sensitivity, whereas the specificity of PSA was only 65% in the same population (Leman et al., 2007). More importantly, in contrast to PSA, ECPA-2 is able to discriminate men with non-organ-confined prostate cancer from those with organ-confined diseases. Although additional validation studies are needed to show the performance of ECPA-2 in a more representative population, these results lend support to the development of a more accurate blood-based assay to identify aggressive prostate cancer.

2.4 uPA/uPAR

A wealth of reports suggest a key role for the urokinase-type plasminogen activator and its receptor (uPA/uPAR) in invasion and metastatic dissemination (Duffy, 2004). uPA is a member of the serine protease family synthesized and secreted as a pro-enzyme, whose activation is markedly accelerated upon binding with high affinity to specific membrane-bound or soluble cell surface uPAR. Once activated, the uPA/uPAR system efficiently converts plasminogen into plasmin, a protease which then modulates extracellular matrix degradation, tumor cell invasion and growth factor activation (Duffy, 2004). In prostate cancer, overexpression of uPA and uPAR (transcripts and proteins) have been reported in tumor tissues suggesting that both proteins could be associated with tumor progression. Immunohistochemical studies have shown an incremental increase in uPA/uPAR expression from benign epithelium to primary organ-confined prostate cancer, to disease extending beyond the prostate capsule, and to bone metastases (Cozzi et al., 2006; Gavrillov et al., 2001; Pulukuri et al., 2007; Usher et al., 2005). In addition, overexpression of uPA and its inhibitor PAI-1 are associated with aggressive prostate cancer recurrence in men treated with radical prostatectomy (Gupta et al., 2009). Elevated circulating levels of uPA and/or uPAR have been associated with advanced prostate cancer and bone metastases (Hienert et al., 1988a; Hienert et al., 1988b; Miyake et al., 1999). Shariat et al. have recently reported that plasma levels of uPA and uPAR are not only higher in men with prostate cancer than in healthy controls, but decrease significantly after prostatectomy (suggesting that direct local production by malignant cells significantly contributes to increased uPA and uPAR circulating levels of these markers in patients), then increase with disease progression (Shariat et al., 2007). Of note, higher preoperative uPA and uPAR were both significantly associated with shorter progression PSA doubling times, failure to respond to salvage local

radiation therapy, and /or development of distant metastases (Shariat et al., 2007). Larger studies are needed to validate the promising role of uPA and uPAR as biomarkers of aggressive prostate cancer.

3. DNA biomarkers

3.1 Epigenetic markers

Epigenetic alterations, i.e., alterations in gene expression without changes in the DNA sequence, include global genomic hypomethylation, promoter hypermethylation of CpG islands and loss of imprinting. The most common somatic genome alteration during prostate cancer development appears to be the hypermethylation in the regulatory region of certain genes, most commonly in the promoter of the π -class glutathione-S-transferase (*GSTP1*) gene (Lee et al., 1994). *GSTP1* is a member of a large family of glutathione transferases that protect DNA from free radicals (Hayes & Strange, 1995). Men with a positive preoperative serum analysis for *GSTP1* CpG island hypermethylation were at significant risk to experience PSA recurrence within the first several years following radical prostatectomy (Bastian et al., 2005). A high frequency of *GSTP1* methylation in the urine of men with high-stage cancer was also recently reported (Woodson et al., 2008). Other candidate genes have been examined for hypermethylation along with *GSTP1*. A recent study suggested that men with advanced prostate cancer and biochemical recurrence experience a significant increase in promoter hypermethylation between initial diagnosis (first blood analysis) and time to progression (second blood analysis) in the four genes with the highest methylation frequencies (*GSTP1*, *APC*, *RAR β 2* and *RASSF1 α*) in prostate cancer patients compared to age-matched controls (Roupert et al., 2008). This study suggests that multiple gene methylation analysis in circulating cell DNA could be a good biomarker for early detection of prostate cancer recurrence.

3.2 Gene fusion proteins

Based on a bioinformatics strategy Tomlins et al. described for the first time in prostate cancer a series of genetic rearrangements between the 5'-untranslated region of TMPRSS2 (21q22) and some members of the ETS family of transcription factors, such as ERG (21q22), ETV1 (7p21) and ETV4 (17q21), which have important roles in several oncogenic pathways (Tomlins et al., 2005). Approximately 50% of prostate cancers from serum PSA-screened cohorts harbor recurrent gene fusions (Kumar-Sinha et al., 2008), which can be detected by fluorescent *in situ* hybridisation (FISH). Conflicting results have been reported regarding the prognosis value of prostate cancer harboring TMPRSS2:ERG gene fusions. Earlier studies reported associations with high stage, metastasis, and prostate cancer-specific death (Attard et al., 2008; Demichelis et al., 2007; Nam et al., 2007), but more recent reports found no association with outcome (Gopalan et al., 2009; Leinonen et al., 2010; Mehra et al., 2007), an association with favorable outcome (Saramaki et al., 2008), or a similar percentage of TMPRSS2:ERG gene fusion in minute and nonminute adenocarcinomas (Albadine et al., 2009), all suggesting its lack of value as a marker of aggressive prostate cancer. The analysis of the relationship between TMPRSS2:ERG fusion and morphological features of prostate cancer has produced diverging results. Most studies have found no statistically significant association between TMPRSS2:ERG rearrangement and Gleason score, while some have demonstrated an association with either higher (Attard et al., 2008; Demichelis et al., 2007)

or lower Gleason scores (Fine et al., 2010; Gopalan et al., 2009). Taken together, it seems like the TMPRSS2:ERG fusion gene is an early event related to development of prostate cancer rather than a marker for progressive disease. Of note, the TMPRSS2:ERG fusion has potential for noninvasive prognosis of prostate cancer. Although RNA-based urinary tests demonstrate in general a high specificity and sensitivity to detect prostate cancer, no significant relationship was found between the presence of fusion transcripts and Gleason score or clinical stage (Hessels et al., 2007; Rice et al., 2010).

3.3 Loss of heterozygosity

The loss of heterozygosity (LOH) is a frequent genetic alteration in prostate cancer, in particular on chromosome arms 7q, 8p, 10q, 12p, 13q, 16q, 17q and 18q (Dong, 2006). Studies on chromosomal deletions of 8p22 by fluorescence in situ hybridization technique revealed 8p22 deletion to be the strongest parameter to predict disease progression in patients undergoing surgery (Matsuyama et al., 2001). If some LOH have been shown to be associated with early stages of prostate cancer (Lu & Hano, 2008), others seem to indicate the presence of tumor suppressor genes whose inactivation is correlated with aggressive and metastatic tumors (Dong et al., 2000; Kibel et al., 2000; Matsuyama et al., 2007). A recent study reported the development of a noninvasive method to detect early stages of prostate cancer using LOH analysis of 7q31, 8p22, 12p13, 13q14, 16q23.2 and 18q21. Indeed LOH could be found in cells from urine obtained by prostatic massage (Thuret et al., 2005). In patients who underwent radical prostatectomy, LOH was confirmed from the prostatic tissue with a concordance of 86%. This noninvasive approach warrants further investigation to bring prognostic information on prostate cancer aggressiveness.

4. RNA biomarkers

4.1 PCA3

PCA3 (formerly known as DD3) is a non-coding RNA very prostate specific (Bussemakers et al., 1999; de Kok et al., 2002). PCA3 mRNA levels can be measured in the urine specimens and several studies have shown that the PCA3 score is superior to serum PSA for predicting biopsy outcome (Groskopf et al., 2006; Haese et al., 2008; van Gils et al., 2007). The relationship between PCA3 score and parameters of cancer aggressiveness has also been studied and differ. Some studies report a positive relationship between PCA3 scores and parameters of more serious disease (Nakanishi et al., 2008; Whitman et al., 2008), while other studies could not find such a relationship (Hessels et al., 2010). Further studies are requested to evaluate the potential of PCA3 testing as prognostic test for prostate cancer.

4.2 AMACR

α -methylacyl-CoA racemase (AMACR) is a catalyst in the peroximal beta-oxidation of branched chain fatty acids found in dietary sources (Wanders et al., 2001), such as red meat and dairy products, the consumption of which has been associated with increased prostate cancer risks (Hsing & Chokkalingam, 2006). AMACR has been identified as a potential biomarker based on its overexpression in localized prostate cancer as compared to benign prostate epithelium (Luo et al., 2002; Rhodes et al., 2002; Rubin et al., 2002). In fact, immunostaining for AMACR is commonly performed in prostate biopsies to help distinguish benign from malignant tissue. Of note, AMACR expression was found consistently lower both at the transcriptional (cDNA expression arrays and RT-PCR) and at

the protein level (immunohistochemistry and western-blot) in metastatic prostate cancer compared to localized prostate cancer (Kuefer et al., 2002; Rubin et al., 2004). An association between low AMACR protein expression at diagnosis and an increased risk of biochemical recurrence and fatal prostate cancer was reported in patients diagnosed with a localized prostate cancer who underwent radical prostatectomy or not (Rubin et al., 2005). Recent findings from the same group confirmed that down-regulation of AMACR expression is associated with poorer outcomes in a cohort of 920 men diagnosed with prostate cancer. However the lack of statistical significance suggests that tumor AMACR expression at diagnosis is not a useful prognostic biomarker for lethal disease after treatment (Barry et al., 2011). Although AMACR protein can be detected in urine by western-blot, its concentration is low in serum, making the development of a serum test difficult (Rogers et al., 2004). Circulating concentrations of AMACR mRNA in urine or serum quantified by RT-PCR have been found elevated in patients but these pilot studies are limited to small series (Zehentner et al., 2006; Zielie et al., 2004).

4.3 MicroRNAs

MicroRNAs are small RNAs found to regulate mRNA function by modulating both mRNA stability and the translation of mRNA into protein. Their expression is commonly altered in solid tumors and multiple microRNAs have been shown to have oncogenic properties or act like tumor suppressor genes. Besides their therapeutic potential, microRNAs hold unique characteristics that herald them as ideal tumor markers including their stability and ease of detection (Heneghan et al., 2010). Despite the large body of work that has been published to date, only limited information is available regarding the expression levels of specific microRNAs in relation to the aggressiveness of prostate cancer. Taking advantage of the stability of tumor-derived microRNAs in circulating blood, Mitchell and co-workers found a remarkably higher level of miR-141 (46-fold increase) in a patients with metastatic prostate cancer compared to healthy control men (Mitchell et al., 2008). The first evidence of a possible prognostic relevance of microRNAs in prostate cancer was obtained from a study examining the tissue expression of 40 patients undergoing prostatectomy. The increased expression of miR-135b and miR-194 was associated with biochemical recurrence within 2 years of surgery (Tong et al., 2009). Another study, conducted on matched tumor and adjacent normal tissues obtained from 76 patients, found that high expression of miR-96 was associated with cancer recurrence after radical prostatectomy, and that prognostic information was confirmed by an independent tumor sample set from 79 pateints (Schaefer et al., 2010). The miR-221 expression is also progressively reduced in aggressive prostate cancer and metastasis and predicts clinical recurrence in patients (n=92) undergoing radical prostatectomy (Spahn et al., 2010). More recently, miR-143 and miR-145 were identified as being associated with bone metastasis of prostate cancer and involved in the regulation of epithelial-mesenchymal transition (Peng et al., 2011). Interestingly, the loss of miR-101 expression during cancer progression in human tumors has been associated with overexpression of histone methyltransferase EZH2 (enhancer of zeste homolog 2) (Varambally et al., 2008). Amounts of both EZH2 mRNA and EZH2 protein are increased in metastatic prostate cancer; in addition, clinically localized prostate cancers that express higher concentrations of EZH2 show a poorer prognosis (Varambally et al., 2002). In cancer cell lines, the expression and function of EZH2 are inhibited by miR-101 (Varambally et al., 2008).

Thus, dysregulated expression of EZH2 may be involved in the progression of prostate cancer, and miR101 might represent a marker that distinguishes indolent prostate cancer from those at risk of lethal progression

5. Other potential biomarkers

5.1 Metabolomics

Metabolite profiling or metabolomics, the analysis of endogenous metabolites in a biological system was recently suggested to be a promising approach to identify novel metabolites or their changes (Fredolini et al., 2010). In practice, however, analysis of the metabolome is complex because of the large range of detectable metabolites. By screening 110 samples from men's urine and blood and 42 tissue samples, Chinnaiyan and collaborators recently identified 1,126 metabolites. They identified 87 that distinguish normal prostate from prostate cancer, then narrowed down the list to 6 whose levels were higher in samples linked to localized prostate cancer and higher still in metastatic disease (Sreekumar et al., 2009). Sarcosine, an *N*-methyl derivative of the amino acid glycine, was identified as a differential metabolite that was highly increased during prostate cancer progression to metastasis. Surprisingly, the authors also provided evidence using cell cultures for a functional role of sarcosine in promoting invasive properties in these cells, whereas lowering the level of the enzyme producing sarcosine reduces invasiveness (Sreekumar et al., 2009). The potential role of urinary was reevaluated in another study, which showed that sarcosine in urine after digital rectal examination fails as a marker in prostate cancer detection and identification of aggressive tumors (Jentzmik et al., 2010). In addition to this work, the same group showed no correlation with sarcosine level in tissues and tumor stage, tumor grade or biochemical recurrence in 92 samples obtained after radical prostatectomy (Jentzmik et al., 2011). Although the lack of metastatic tissue samples was a limitation, this study establishes that sarcosine measurement in prostate tissue is not suitable to predict cancer aggressiveness or biochemical progress.

5.2 Disseminated tumor cells

The shedding of tumor cells into the circulation is a necessary condition for metastasis dissemination and the clinical relevance of the detection of disseminated tumors cells (DTCs) in bone marrow (the most prominent metastatic site in prostate and breast cancer) or in peripheral blood of patients free of apparent metastasis is under investigation. So far, only large breast cancer studies have confirmed the independent prognostic value of the bone marrow status (Berg et al., 2007). Recent studies have demonstrated an association between DTCs in bone marrow at diagnosis of nonmetastatic prostate cancer (Berg et al., 2007; Kollermann et al., 2008). Although a DTC-positive bone marrow status was associated with grading and increased risk of metastasis, the study by Berg et al. on 266 patients did not find a correlation of DTC detection and survival (Berg et al., 2007). In contrast, Köllermann et al. demonstrated the prognostic relevance of DTCs in bone marrow patients with clinically localized prostate cancer submitted to neo-adjuvant hormonal therapy followed by radical prostatectomy and a median follow-up of 44 months (Kollermann et al., 2008). This study is the first one on a large series of patients with sufficient long follow-up to clearly demonstrate an adverse prognostic effect of the presence of DTCs at the time of initial diagnostic.

Markers	Strategy of Detection	Comments
PSCA	RT-PCR (blood), Protein expression (tissue)	Potential therapeutic target
PSP94	ELISA (blood), Protein expression (tissue)	One of the major secretory proteins of the prostate gland
ECPA/ECPA-2	ELISA (blood), Protein expression (tissue)	
uPA/uPAR	ELISA (blood), Protein expression (tissue)	uPAR expression in DTCs (bone marrow, peripheral blood), Potential therapeutic target
Epigenetic markers (eg. GSTP1)	Methylation specific PCR (blood, urine)	Potential Multiplex test with other urine biomarkers
Gene fusion proteins (eg. Tmprss2 :ERG)	RT-PCR (urine) FISH (tissue)	Potential Multiplex test with other urine biomarkers
Loss of heterozygoty	PCR (blood, urine)	
PCA3	Transcription-mediated amplification assay (urine)	Potential Multiplex test with other urine biomarkers
AMACR	RT-PCR (blood, urine) Protein expression (tissue)	Potential Multiplex test with other urine biomarkers, Potential therapeutic target
MicroRNAs	RT-PCR (blood, urine, tissue)	Potential therapeutic targets
Metabolomics	Profiling (urine, blood)	
Disseminated Tumor Cells	Enumeration (blood, bone marrow)	

Table 1. Potential biomarkers and their strategy of detection

Despite bone marrow analysis provides important information, peripheral blood studies are more acceptable in the clinical management than invasive BM aspirations. However, identification of circulating tumor cells (DTCs) require extremely sensitive analytical methods that are usually combined with enrichment procedures. Although promising results from patients with advanced stages demonstrate the value of CTCs technology (currently evaluated and validated in clinical trials as a predictor and surrogate endpoint of

treatment response), studies on patients at earlier stages are hampered by the low CTC counts. A recent study from Haber and collaborators shows that tumor cells obtained from the blood of cancer patients were monitored before and after surgery, most circulating cells rapidly declined shortly after surgery while others persisted months thereafter, suggesting that postoperative CTCs might derive from preestablished non prostatic sites of disease that continue to shed CTCs into the circulation (Stott et al., 2010). If confirmed, these observations support the potential application of CTC monitoring as a marker of invasive localized disease before the establishment of viable metastatic lesions.

6. Conclusion

We have here attempted to give some examples of potential DNA-based, RNA-based and protein-based markers of aggressiveness in prostate cancer. Comparisons between studies are often difficult because of some inconsistencies between study cohorts, collection methods and handling of samples. It is unlikely that a single biomarker (evaluated on conventional approach looking at a single molecular predictor significantly up- or down-regulated) will provide the information requested to tell how aggressive a diagnosed prostate cancer is. New research methods (proteomics, metabolomics...) are also emerging, and high-throughput technologies will facilitate biomarker discovery. Therefore, future advances in this field will probably have to integrate proteomics, transcriptomics and multiplex approaches and identify combinations of multiple biomarkers in order to improve the characterization of aggressive prostate cancers.

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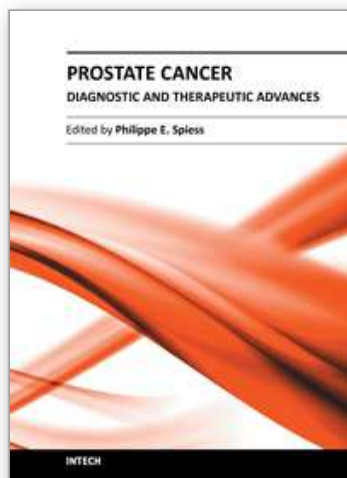
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In this book entitled "Prostate Cancer - Diagnostic and Therapeutic Advances", we highlight many of the significant advances made in our treatment armamentarium of prostate cancer. The book is subdivided into four sections termed: 1) novel diagnostic approaches, 2) surgical treatments options, 3) radiation therapy and its potential sequelae, and 4) medical management and its treatment complications. After reading the present book, readers will be very familiar with the major clinical advances made in our multifaceted treatment approach to prostate cancer over the past decade. This book is a tribute to our pioneering urologists and allied healthcare professionals who have continually pushed forward our traditional therapeutic envelope.

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