View metadata, citation and similar papers at core.ac.uk

brought to you by CORE

provided by IntechOpen

# We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

**4,800**
Open access books available

**122,000**
International authors and editors

**135M**
Downloads

Our authors are among the

**154**
Countries delivered to

**TOP 1%**
most cited scientists

**12.2%**
Contributors from top 500 universities

CLARIVATE ANALYTICS BOOK CITATION INDEX INDEXED

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index in Web of Science™ Core Collection (BKCI)

## Interested in publishing with us?
## Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

1

# Prostate Cancer: Essential Diagnostic and Therapeutic Considerations

Paul Bradley and Philippe E. Spiess
*Department of Urologic Oncology, Moffitt Cancer Center, Tampa, FL USA*

## 1. Introduction

The potential impact imparted by prostate cancer on our society is immense. In this chapter, we provide a general overview of current concepts, diagnostic advances, and novel therapeutic approaches to the management of prostate cancer. It is widely reported that prostate cancer is the most common malignancy diagnosed in U.S. males. The current lifetime risk of developing prostate cancer is 17%, with an estimated lifetime cancer-specific mortality risk of 3%. The diagnosis of prostate cancer rapidly increased in the mid-1980s, with the advent of the serological biomarker prostate specific antigen (PSA) which has played a pivotal role in the screening and early detection of prostate cancer worldwide.

From what was almost uniformly a poor prognostic malignancy associated with highly morbid therapies, prostate cancer emerged as a potentially curable disease, with state of the art diagnostic and therapeutic approaches. Advancements in the last 30 years have redefined the surgical approach of localized prostate cancer with minimally invasive surgical approaches for the most part being our primary treatment approach. Additionally radiotherapy techniques have been refined increasing the efficacy and limiting the toxicity to adjacent organs. New systemic and vaccine therapies have most recently emerged as effective approaches to advanced disease.

## 2. Prostate cancer screening

Prostate cancer screening has evolved since the initial introduction of serum PSA in our screening armamentarium. The discovery of PSA in the 1980s along with an appreciation of its prognostic significance has greatly impacted patient education and surveillance recommendations. Over the last two decades, a stage migration has occurred in favor of small volume, localized disease which we believe is in large part as a direct consequence of the utilization of serum PSA screening. Between 1986 and 1999, there has been a dramatic reduction in the incidence of locally advanced, high volume disease for the similarly proposed reasons. The Prostate, Lung, Colorectal, and Ovary (PLCO) cancer trial of the National Cancer Institute (NCI) was designed to evaluate the effectiveness of prostate cancer screening. It began accruing patients between 1993 and 2001. The study demonstrated a 22% increase in the detection of prostate cancer at 7 years and a 17% increase at 10 years in the patient cohort undergoing annual digital rectal examination

(DRE) and PSA. Despite these findings, the number of deaths between the two study arms were not statistically significant suggesting that screening did not impart a survival benefit with short to intermediate follow-up. The European Randomized Study of Screening for Prostate Cancer (ERSPC) was a similarly designed prospective randomized trial that enrolled 162,387 men. The authors concluded that to prevent a single death from prostate cancer, 1410 men needed to be screened and 48 needed to be treated nevertheless this was a positive study in terms of demonstrating the survival imparted from prostate cancer screening.

Screening using PSA has evolved in recent years by looking at various PSA isoforms and exploring new serological and urinary biomarkers. The evaluation of unbound PSA or free PSA has been proposed in an attempt to improve cancer screening efforts while reducing the number of patients undergoing transrectal prostatic biopsies with its inherent risks, discomfort, and associated healthcare costs. Other novel markers have as well been considered including Prostate Cancer Antigen 3 (PCA3) which was first cited as a potential biomarker for prostate cancer in 1999. It differs from PSA in that it is acquired from the urine following a prostatic massage. Among prostate cancer patients, PCA3 has been found to be upregulated up to a 66-fold in 95% of patients. Although a large validation study has yet to be completed, PCA3 appears to show promise as an adjunctive screening tool to PSA. Additionally, there is an isoform of PSA called proPSA that is mostly found within the peripheral zone of the prostate and within the circulatory system. Multiple variants of this isoform exist with the [-2]proPSA showing the most compelling results pertaining to screening for prostate cancer. [-2]proPSA is the most prevalent form found within prostate cancer cells. Elevations of this variant have also been found to directly correlate with the underlying Gleason score of the tumor. Despite these promising data, the clinical use of these biomarkers remain to be defined until more robust clinical studies validate its superiority versus total serum PSA.

Evolving data pertaining to screening biomarkers and two recent large prospective clinical trials have fueled the controversy regarding screening guidelines and recommendations put forth by various medical governing bodies and organizations. According to the PLCO trial, harm associated directly with screening remains relatively low. DRE can lead to bleeding or significant discomfort/pain in 0.3 per 10,000 screened men. The blood procurement (i.e. phlebotomy) required in PSA screening imparts an associated risk of dizziness, bruising, or hematoma in 26.2 per 10,000 screened men along with 3 episodes of fainting per 10,000. Most importantly, complications from the resulting transrectal prostatic biopsy occurred in 68 per 10,000 cases which included infection, bleeding, and voiding difficulties. In addition, the overtreatment of clinically insignificant tumors which would likely never be biologically aggressive may for the most part only expose patients to the inherent risks and potential morbidities of localized prostate cancer treatments including incontinence and/or erectile dysfunction.

Four organizations currently provide some degree of guidance on the topic of screening. The American Urologic Association (AUA) and the American Cancer Society (ACS) both recommend giving men the option of screening starting at the age of 50 using the combination of PSA and DRE and starting earlier in higher risk men (e.g. patients with first and/or second degree relatives with prostate cancer, certain racial ethnicities such as African Americans). The National Comprehensive Cancer Network (NCCN) has some of the most definitive screening guidelines which include recommending a single total serum PSA test at the age of 40 followed by another PSA at the age of 45, with annual screening

thereafter at the age of 50. Prostatic biopsies are recommended based on the NCCN guidelines when a total serum PSA is greater than 2.5 ng/mL. On the contrary, the United States Preventative Services Task Force (USPSTF) provide no guidelines stating that present research on the subject matter is inconclusive and in fact their position statement is against screening men over the age of 75.

## 3. Chemoprevention

Not surprisingly, along with the rise in the incidence of prostate cancer interest in prostate cancer prevention has come to the forefront. The Selenium and Vitamin E Cancer Prevention Trial (SELECT) is the largest chemoprevention trial in prostate cancer. They enrolled 35,534 participants that were randomized to three arms (one, both, or none of the supplements). Several smaller trials had previously shown a possible reduction in the incidence of prostate cancer among patients taking these proposed chemoprevention agents nevertheless it was felt a larger study was required to more definitely address this clinical question. Unfortunately, the final analysis of this study did not demonstrate a decrease in the risk of developing prostate cancer in either of the chemoprevention arms. In fact, a small increase in the diagnosis of prostate cancer was noted in the group taking vitamin E alone in addition to an increase in the incidence of diabetes among those taking selenium. At this time, the men in this trial have been instructed to discontinue taking these supplements and will be followed for the next three years to evaluate the long-term sequelae of this chemoprevention trial.

The concept of chemoprevention of prostate cancer has gained popularity in the last decade with the results of two large prospective studies (PCPT and REDUCE trials). Both of these trials assessed the impact of selective androgen blockade through 5-α reductase inhibition in an attempt to prevent prostate carcinogenesis. The two trials differed in their design, with the PCPT trial recruiting healthy men with no increased risk of developing prostate cancer whereas the REDUCE trial included men with a higher relative risk of developing prostate cancer. Both studies were positive in that they demonstrated a reduction in the overall incidence of prostate cancer among men receiving an oral 5-α reductase inhibitor.

The PCPT trial evaluated the specific effects of finasteride, with men receiving this agent being 24.8% less likely to develop prostate cancer. The trial however revealed the alarming concern of an increased incidence of higher grade tumors (Gleason 7-10 tumors) in the treatment arm. One proposed explanation for this was postulated to be the change in the appearance of the prostatic cytoarchitecture and cellular morphology as a result of the hormonal effects of finasteride. Another theory is that finasteride selectively inhibits lower grade tumors and shrinks the overall size of the prostatic gland resulting in an overall increase in the number of higher grade cancers detected within a now smaller gland.

The REDUCE trial differed from the PCPT trial in that the inclusion criteria were modified to target men with risk factors for developing prostate cancer as well as using a different 5-α reductase inhibitor (dutasteride) in the treatment arm. This trial included 8,200 men between the ages of 50 and 75 years of age. Men younger than 60 had a baseline total serum PSA between 2.5 and 10 ng/mL whereas older men had a total serum PSA value between 3.0 and 10 ng/mL. Additionally, the participants had a prostate biopsy within 6 months of enrollment demonstrating no evidence of cancer, atypical small acinar proliferation (ASAP), or high-grade prostatic intraepithelial neoplasia. Men were randomized to placebo or the dutasteride treatment arm. The study's primary treatment

endpoint was the reduced risk of developing prostate cancer, with the dutasteride treatment arm having a 22.8% relative risk reduction and no increased incidence of higher Gleason grade tumors within the treatment arm.

## 4. Patient risk stratification

With the increased incidence of prostate cancer cases detected in recent years, a new therapeutic dilemma has arisen in that clinicians have contemplated whether a subset of tumors were clinically insignificant and could be surveilled rather than undergo definitive local therapy. In this regard, risk stratification models have been proposed as a means to tailor treatment recommendations based on the biological aggressivity and risk of progression of the tumor. The Partin tables were first proposed in 1993 in which they developed a cancer specific predictive model based on total serum PSA, biopsy Gleason score, and clinical stage. Patients and clinicians benefited from the use of the Partin tables to counsel and tailor patient treatment recommendations. The D'Amico risk stratification is a simplified version of the Partin tables dividing patients into one of three prognostic categories based on the same three pre-treatment diagnostic parameters (PSA, biopsy Gleason score, and clinical stage). Using the D'Amico risk groups, patients can be stratified into the low, intermediate, and high risk groups serving as an important clinical tool for guiding therapeutic options and suitability for clinical trials.

## 5. Treatment recommendations

The treatment modalities suitable for localized prostate cancer continue to evolve and expand, with novel technological advances. Dr. Walsh's pioneering work in the anatomical and surgical approach to the radical prostatectomy resulted in a dramatic decline in the reported morbidity of this procedure. Thereafter, Schuessler et al. published the first description of a laparoscopic radical prostatectomy in 1997 with the first case performed in 1991. This technique was however initially abandoned due to its steep learning curve and long operating times, without a clear benefit imparted to patients. With advances in laparoscopic skills and instrumentation, this minimally invasive approach was resurrected before being integrated with modern robotic assisted techniques. Today, nearly 85-90% of all radical prostatectomies are performed using a robotic assisted technique. The questions currently being raised with this technology relates to the expense of this procedure and whether it in fact imparts a clear benefit versus open surgery in terms of cancer control, continence, and potency preservation.

Radiotherapy for localized prostate cancer has evolved by leaps and bounds. External beam radiation therapy (XRT), brachytherapy, and high dose rate (HDR) implant therapy can all be utilized as first line treatment options for localized prostate cancer. Historically, XRT began as a four field box technique fractionating doses over several weeks. This was later replaced by three dimensional conformal radiation therapy and further refined using intensity modulated radiation therapy to limit the dose/toxicity delivered to surrounding tissues while maximizing the therapeutic effective dose delivered to the prostate.

Interstitial brachytherapy can be performed using three different radioisotopes (Iodine 125, Palladium 103, and Cesium 131). Each of these isotopes have different half-lives although all three have reported similar cancer specific outcomes. Interstitial brachytherapy as a monotherapy has become a viable treatment alternative to radical prostatectomy or XRT

among patients in the low to intermediate D'Amico risk groups. Using this technique, radioactive seeds are implanted within the prostate under transrectal ultrasound guidance through the perineum and under general anesthesia. Contraindications to interstitial brachytherapy include patients with prostate sizes greater than 60 grams, a previous transurethral resection of the prostate, or significant baseline voiding complaints. The prostate size limitation imparted by brachytherapy result from the fact: (1) large prostates are unable to be completely treated due to the interference by the pubic bone during implantation and (2) patients with large prostates being at increased risk of post-implantation urinary retention. Despite these limitations, brachytherapy remains a popular treatment modality among low D'Amico risk patients, with comparable oncological outcomes to other treatment modalities.

In addition to surgery and radiotherapy, novel ablative therapies including cryotherapy and high-intensity focused ultrasound (HIFU) have emerged as primary local treatments to prostate cancer. Cryotherapy can be used as a primary treatment to localized disease but remains most frequently used as a salvage local therapy. HIFU has gained increasing popularity in recent years as a potential new local treatment for prostate cancer. HIFU was first proposed as a treatment option for prostate cancer in 1999 and entails the use of ultrasonic waves administered using a transrectal ultrasound probe technique. This approach provides an alternative to more traditional modalities such as surgery or radiotherapy. Although not FDA approved in the United States, this technology has been used in many European countries including France and Germany for several years. Long-term data evaluating the oncological outcome of HIFU and contrasting it to other currently available treatment modalities are lacking.

HIFU has also been evaluated as a form of focal therapy for prostate cancer. Unfortunately, data evaluating focal therapy in general have been disappointing. Up to 21% of patients treated by focal therapy may be undertreated according to a study by Katz el al. evaluating post-prostatectomy specimens. All patients in this study who met the original focal therapy criteria would have had a significant secondary tumor missed, with 58.3% of these patients having a final pathological Gleason score of ≥ 7 and 25% exhibiting a final pathological stage of pT3. Based on this and other compelling data, focal therapy appears to be an ineffective therapy in its current applications until we develop better imaging modalities for detecting clinically significant prostate cancer foci within an individual patient's prostate.

The use of neoadjuvant and adjuvant androgen deprivation therapy (ADT) has also been thoroughly investigated. The CaPSURE trial found a 2.6 fold increase in cardiovascular events in men treated with both ADT and RRP compared to RRP alone. Even though one could conceptually see how preoperative ADT would be beneficial, it has never been shown to improve the cancer specific outcomes of patients undergoing RRP (even amongst patients falling within the high risk D'Amico group).

Active surveillance has gained increasing popularity as a treatment alternative for a subset of patients with prostate cancer over the past decade. This has likely resulted from the previously mentioned stage migration of prostate cancer, with a significant proportion of patients presenting with clinically "insignificant" prostate cancer. Debate continues to ensue on the exact therapeutic role and which patients are ideally suited for active surveillance; nevertheless, its viability as a treatment alternative for a significant subset of prostate cancer patients is undeniable.

The management of locally advanced prostate cancer can constitute a therapeutic dilemma for clinicians. Treatment alternatives for these patients include: (1) XRT and adjuvant ADT

for 2 to 3 years and (2) RRP +/-neoadjuvant/adjuvant chemohormonal therapy preferably as part of a clinical trial. Recent data from the Memorial Sloan Kettering Cancer Center on the surgical management of locally advanced and high-risk prostate cancer have been encouraging. In this study, 4,708 post-prostatectomy men were retrospectively evaluated and categorized as high-risk based on eight different definitions. Depending on the definition used, between 3 to 38% of these patients were considered high-risk. Interestingly, 22-63% of these men had pathologically organ confined cancer and a 5 year relapse-free probability of 49-80%. This suggests that men with traditionally high-risk disease may still be candidates for potentially curative surgical resection.

There have as well been major advances made in the management of hormone-refractory and metastatic prostate cancer. In this regard, taxotere remains the first line agent for the management of hormone refractory, metastatic prostate cancer. In addition, exciting new data pertaining to prostate cancer include vaccine therapy using Sipuleucel T, abiraterone, and cabazitaxel; all of which may potentially redefine our therapeutic approach to the management of advanced disease.

## 6. Conclusions

Significant advances have been made in the field of prostate cancer research and clinical/surgical care. Nevertheless, many unanswered questions remain. In addition, the true survival benefit imparted by prostate cancer screening remains a hotly debated issue within the scientific literature. Emerging prostate cancer tumor markers such as PCA3 and [-2]proPSA have not yet been shown to be superior to the current biomarker benchmark PSA. Advancements in laparoscopic technique and technology will hopefully continue to reduce the morbidity associated with radical prostatectomy. Lastly, new therapeutic agents have been discovered which have redefined the management of advanced prostate cancer. We hope the present chapter has highlighted some of the key clinical concepts and treatment principles pertaining to this highly prevalent malignancy.

The aim of the present textbook is to provide an in depth understanding of the intricacies encompassing the diagnosis and management of prostate cancer and encapsulate some of the current exciting areas of active clinical/translational research within our scientific community.

## 7. References

Andriole GL et al. (2009). Mortality Results from a Randomized Prostate-Cancer Screening Trial. *N Engl J Med*, Vol. 360, No .13, (Mar 2009), pp. 1310-1319

Andriole GL, Bostwick DG, Brawley OW, Gomella LG, Marberger M, Montorsi F, Pettaway CA, Tammela TL, Teloken C, Tindall DJ, Somerville MC, Wilson TH, Fowler IL, Rittmaster RS; REDUCE Study Group. (2010). The Effect of Dutasteride on the Risk of Prostate Cancer. *N Engl J Med*, Vol. 362, No. 13, (Apr 2010) pp. 1192-202

AUA Clincial Guidelines. (2009). Prostate-Specific Antigen Best Practices Statement

Chan TY, Mikolajczyk SD, Lecksell K et al. (2003). Immunohistochemical staining of prostate cancer with monoclonal antibodies to the precursor of prostate-specific antigen. *Urology,* Vol. 62, No. 1, (Jul 2003), pp. 177-81

Chapelon JY, Ribault M, Vernier F, Souchon R, Gelet A. (1999). Treatment of localised prostate cancer with transrectal high intensity focused ultrasound. *Eur J Ultrasound*, Vol. 9, No. 1, (Mar 1999), pp. 31-8

Civantos F, Soloway MS, Pinto JE. (1996). Histopathological effects of androgen deprivation in prostatic cancer. *Semin Urol Oncol,* Vol. 14, No. 2, (May 1996), pp. 22-31.

D'Amico AV, Whittington R, Malkowicz SB et al. (1998). Biochemical outcome after radical prostatectomy, external beam radiation therapy, or interstitial radiation therapy for clinically localized prostate cancer. *JAMA*, Vol. 280, No. 11, (Sept 1998), pp. 969-74

Hessels D, Klein Gunnewiek JM, van Oort I et al. (2003). DD3(PCA3)-based molecular urine analysis for the diagnosis of prostate cancer. *Eur Urol*, Vol. 44, No. 1, (July 2003), pp. 8-15

Jemal A, Tiwari RC, Murray T, et al. (2004). American Cancer Society: Cancer statistics 2004. *CA Cancer J Clin*, Vol. 54, No. 1, (Jan-Feb 2004), pp. 8-29

Katz B, Srougi M, Dall'oglio M, Nesrallah AJ, Sant'anna AC, Pontes J Jr, Reis ST, Sañudo A, Camara-Lopes LH, Leite KR. (2011). Are we able to correctly identify prostate cancer patients who could be adequately treated by focal therapy? *Urol Oncol*, (Mar 2011), Ahead of publication.

Klein EA, Thompson IM, Lippman SM, Goodman PJ, Albanes D, Taylor PR, Coltman C. (2001). SELECT: the next prostate cancer prevention trial. Selenum and Vitamin E Cancer Prevention Trial. *J Urol*, Vol. 166, No. 4, (Oct 2001), pp. 1311-5

Mikolajczyk SD, Millar LS, Wang TJ et al. (2000) A precursor form of prostate-specific antigen is more highly elevated in prostate cancer compared with benign transition zone prostate tissue. *Cancer Res*, Vol. 60, No. 3, (Feb 2000), pp. 756-9

Partin AW, Yoo J, Carter HB, Pearson JD, Chan DW, Epstein JI, Walsh PC. (1993). The use of prostate specific antigen, clinical stage and Gleason score to predict pathological stage in men with localized prostate cancer. *J Urol*, Vol. 150, No. 1, (Jul 1993), pp. 110-4

Schuessler WW, Schulam PG, Clayman RV, Kavoussi LR. (1997). Laparoscopic radical prostatectomy: initial short-term experience. *Urology*, Vol. 50, No. 6, (Dec 1997), pp. 854-7

Smith RA, Cokkinides V, Eyre HJ. (2006). American Cancer Society guidelines for the early detection of cancer, 2006. *CA Cancer J Clin*, Vol 56, No. 1, (Jan-Feb 2006), pp. 11-25

Sokoll LJ, Wang Y, Feng Z et al. (2008). [-2]proenzyme prostate specific antigen for prostate cancer detection: a national cancer institute early detection research network validation study. *J Urol*, Vol. 180, No. 2, (Aug 2008), pp. 539-43

Thompson IM, Goodman PJ, Tangen CM, et al. (2003). The influence of finasteride on the development of prostate cancer. *N Engl J Med,* Vol.349, No. 3, (July 2003), pp. 215-224

Tsai HK, D'Amico AV, Sadestsky N et al. (2007). Androgen deprivation therapy for localized prostate cancer and the risk of cardiovascular mortality. *J Natl Cancer Inst,* Vol. 99, No. 20, (Oct 2007), pp. 1516-24

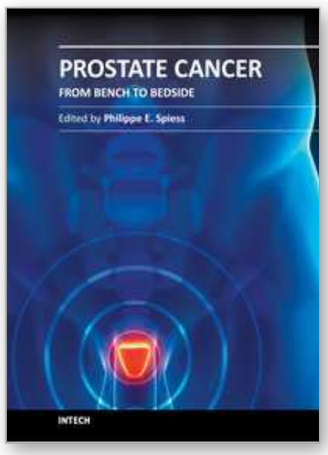
U.S. Preventive Services Task Force Grade Definitions After May 2007. (May 2008). Available from: http://www.uspreventiveservicestaskforce.org/uspstf/gradespost.htm

Walsh PC, Donker PJ. (1982). Impotence following radical prostatectomy: insight into etiology and prevention. *J Urol,* Vol. 128, No. 3, (Sept 1982), pp. 492-7

Yossepowitch O, Eggener SE, Bianco FJ Jr, Carver BS, Serio A, Scardino PT, Eastham JA. (2007). Radical Prostatectomy for Clinically Localized, High Risk Prostate Cancer: Critical Analysis of Risk Assessment Methods. *J Urol*, Vol. 178, No 2, (Aug 2007), pp. 493-9

IntechOpen

IntechOpen




**Prostate Cancer - From Bench to Bedside**

Edited by Dr. Philippe E. Spiess

ISBN 978-953-307-331-6
Hard cover, 528 pages
**Publisher** InTech
**Published online** 25, November, 2011
**Published in print edition** November, 2011

The present textbook highlights many of the exciting discoveries made in the diagnosis and treatment of prostate cancer over the past decade. International thought leaders have contributed to this effort providing a comprehensive and state-of-the art review of the signaling pathways and genetic alterations essential in prostate cancer. This work provides an essential resource for healthcare professionals and scientists dedicated to this field. This textbook is dedicated to the efforts and advances made by our scientific community, realizing we have much to learn in striving to some day in the not too distant future cure this disease particularly among those with an aggressive tumor biology.

**How to reference**

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Paul Bradley and Philippe E. Spiess (2011). Prostate Cancer: Essential Diagnostic and Therapeutic Considerations, Prostate Cancer - From Bench to Bedside, Dr. Philippe E. Spiess (Ed.), ISBN: 978-953-307-331-6, InTech, Available from: http://www.intechopen.com/books/prostate-cancer-from-bench-to-bedside/prostate-cancer-essential-diagnostic-and-therapeutic-considerations

INTECH
open science | open minds

**InTech Europe**
University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

**InTech China**
Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

© 2011 The Author(s). Licensee IntechOpen. This is an open access article distributed under the terms of the Creative Commons Attribution 3.0 License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

IntechOpen

IntechOpen