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The Use of Models to Predict the Presence and Aggressiveness of Prostate Cancer on Prostate Biopsy

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1. Introduction

Prostate cancer is the commonest male malignancy diagnosed in countries in the Western World and it represents the second commonest cause of male cancer-related death. In the United Kingdom in 2008 37,051 new cases of prostate cancer were diagnosed and this malignancy resulted in 10,168 deaths. The morbidity and mortality directly attributable to this common malignancy is considerable, however in some patients the disease is often relatively indolent. Prostate cancer is typically a disease associated with the aging male population however in some cases it may be lethal in a younger subset of men. The degree of benefit to be gained from diagnosing and treating prostate cancer is directly related to the degree of comorbidity and life expectancy of individual men. It is crucial to identify as accurately as possible men at increased risk of prostate cancer in order to improve the diagnostic performance of a prostate biopsy. Moreover it is important to be able to restrict this invasive investigation to men who are likely to benefit from treatment of this malignancy. There are currently concerns that Western clinicians and healthcare providers are over-diagnosing large numbers of men who would otherwise never have been troubled by their clinically undetectable prostate cancer. Moreover there are also concerns that large numbers of men are currently being over-treated for their prostate malignancy, resulting in treatment-related morbidity including surgical and radiotherapy complications such as erectile dysfunction and urinary incontinence. Over the last 25 years urologists and researchers have refined their skills sufficiently well to enable accurate diagnosis of a considerable proportion of prostate cancers. The contemporary challenge however is to diagnose with increased confidence those "clinically significant" cases of prostate cancer which by definition are likely to pose a threat to an individual patient if left undetected. The first part of this chapter outlines the current predictors of prostate cancer on biopsy including clinical, laboratory and research tools. Factors which may help the prediction of prostate cancer on repeat biopsy, as well as current diagnostic performance of prediction tools utilising pre- and post-biopsy data to identify men at high risk of harbouring clinically significant and aggressive prostate cancer are discussed.

2. Prediction of prostate cancer on biopsy

The current method of diagnosing prostate cancer is based upon a triad of digital rectal examination (DRE), serum prostate specific antigen (PSA) measurement, and prostate

biopsy. Indications for performing a prostate biopsy include an abnormal DRE suspicious of malignancy and/or an age-specific abnormal serum PSA. At the present time the majority of cases of prostate cancer in the United Kingdom are identified following "opportunistic screening" or "case finding" whereby men present to their clinician for one of a number of other reasons and then undergo PSA-testing, ideally following appropriate and adequate counselling. A smaller proportion of cases are identified following clinical presentation with lower urinary tract symptoms or with the symptoms related to advanced prostate cancer.

There are a number of problems and controversies surrounding the diagnosis of early organ-confined prostate cancer. Firstly, the PSA test has considerable limitations in its sensitivity and specificity (Schroder et al. 2000), and the result can be difficult to interpret, particularly for non-urologists. Historically a PSA level below 4 ng/mL was considered to be "normal" however over time the upper limits of "normal" PSA were defined in an age-specific manner (table 1) (Oesterling et al. 1993).

More recently the results of the Prostate Cancer Prevention Trial (PCPT) (Thompson et al. 2003) demonstrated that there is no PSA threshold below which one can confidently exclude a diagnosis of prostate cancer. The PCPT trial protocol required "normal" men with very low levels of PSA to be biopsied at the end of the trial and it was observed that 39.2% of men with a PSA 2.1-3.0 ng/mL, 27.7% of men with a PSA 1.1-2.0 ng/mL, and 16.3% of men with a PSA <1.0 ng/mL harboured foci of adenocarcinoma of the prostate (Thompson et al. 2003). Indeed in terms of prostate cancer diagnosis and thresholds for biopsy, the PCPT trial will be remembered more for this remarkable and intriguing observation than for its observations regarding the use of finasteride for prostate cancer chemoprevention.

Age (years)	PSA ng/mL
40-49	2.5
50-59	3.5
60-69	4.5
70-79	6.5

Table 1. Age-specific upper limits of normal PSA.

Whilst some men with a PSA below the currently accepted "normal" age-specific threshold will have prostate cancer, it is also true that many men with a PSA above this threshold will not have prostate cancer as an elevated PSA can be attributable to a number of benign conditions as well apart from the presence of prostate cancer. Considerable efforts have been made to improve the sensitivity and specificity of PSA testing including the adoption of free-to-total PSA ratios, %free PSA, [-2]pro-PSA, PSA density and PSA velocity. The introduction of these parameters into prostate cancer prediction algorithms can only yield modest improvements in the diagnostic accuracy of PSA testing.

At the present time the recommendation to offer a patient a prostate biopsy in order to diagnose early organ confined disease rests with the clinician's interpretation of the PSA result and DRE findings, taking into account the patient's co-morbidity and life expectancy. The final decision to undertake a biopsy is made jointly by the patient and the clinician. This

active engagement of the patient in interpreting a particular PSA result can have both benefits and negative consequences. It enables the patient to be fully engaged in this difficult decision making process. A negative consequence is the generation of a population of patients who may be described as the "worried well" i.e. men with a slightly raised PSA who have either decided not to have a biopsy or who have had negative biopsies but who still have concerns that they might harbour prostate cancer.

A number of pre-biopsy nomograms for prostate cancer risk assessment have been developed by a number of groups to predict the risk of prostate cancer on biopsy and its potential for progression. These risk calculators comprise predictive tables and nomograms and are widely available in the clinic and on the internet. They aim to aid clinicians and patients to decide whether a biopsy is indicated and also may aid treatment selection if cancer is found. The use of such nomograms requires the input of each individual patient's clinical data including parameters such as age, race, family history of prostate cancer, DRE findings, PSA level, and presence/absence of previous negative prostate biopsy (table 2).

Nomogram	Population studied	Factors included in nomogram
Cancer Risk Calculator for prostate cancer	USA	Race Age Family history of prostate cancer DRE findings PSA Previous biopsy results (if performed)
Prostate Risk Indicator	European	Risk indicator 1: Age Family history of prostate cancer Urinary symptoms Risk indicator 2: PSA Risk indicator 3: PSA TRUSS outcome DRE findings Prostate volume

Table 2. Pre-biopsy risk calculators.

The Cancer Risk Calculator for prostate cancer (Thompson et al. 2006) may be used to predict the probability of detecting prostate cancer, including those with a high Gleason Grade. This risk calculator was developed in the USA using a cohort of 5519 men in the placebo group of the PCPT who had an initial low PSA ≤3 ng/mL and had an end-of-study prostate biopsy after seven years of follow-up. This risk calculator has subsequently been adjusted to include the Prostate Cancer Antigen 3 (PCA3) score. PCA3 is a gene encoding a non-translated messenger RNA which is over-expressed in prostate cancer (Deras et al. 2008,

Marks et al. 2007). This test may be useful in evaluating men who already received one set of negative prostate biopsies.

Other adjustments include the incorporation of body mass index, the use of finasteride, percentage free PSA and [-2]pro-PSA. It should be noted that the results of the Cancer Risk Calculator for prostate cancer may not be applicable to all men as most participants in the PCPT were Caucasian, and results may not be applicable to men of other races. In addition, most men in this study underwent a sextant prostate biopsy. This has now been largely superseded by an increase in the number of systematic biopsies taken routinely (Heidenreich et al. 2010). Moreover, the risk calculator is only applicable to men aged 55 or older, without a previous history of prostate cancer and with DRE findings and PSA results less than a year old.

The Prostate Risk Indicator (www.prostatecancer-riskcalculator.com) was developed in Rotterdam and consists of 4 risk calculators, of which the first 3 predict the probability of detecting a prostate cancer (van den Bergh et al. 2008). This nomogram is based on 6288 Dutch men enrolled in the European Randomised Study of Screening for Prostate Cancer (ERSPC) (Schroder et al. 2009). The risk calculator comprises 4 risk indicators, the first 3 of which predict the possibility of a positive prostate biopsy. The first 2 prostate risk indicators produced by this group may be used by the general public whereas the other risk calculators are intended to be used by urologists during patient evaluation.

It is likely that future risk calculators developed for predicting prostate cancer risk upon performance of a prostate biopsy will incorporate the results of novel molecular diagnostic tests such as the detection of prostate cancer specific *TMPRSS2-ERG* fusion genes or *Prostate Cancer Antigen 3* (*PCA3*) in urine sediments. The *TMPRSS2-ERG* fusion gene was discovered to be specifically present in 50% of screened prostate cancer cases although there are conflicting observations regarding its association with advanced disease (Tomlins et al. 2009). A preliminary study on a limited number of patients had shown that the PCA3 test does not perform better than PSA with regards the identification of prostate cancer cases (Nyberg et al. 2010). Nevertheless, a multiplex model including TMPRSS2-ERG, PCA3, sarcosine and Annexin A3 has been shown to significantly improve diagnostic performance for this malignancy with an AUC of 0.86, whereas the AUC ranges from 0.66-0.74 for any of these markers when they are used in isolation (Cao et al. 2010). At the present time an extensive body of research is being conducted with the aim of investigating the potential clinical use of this marker and many other molecular biology tests both before and after undertaking a biopsy to diagnose prostate cancer (Shappell 2008).

Genome wide association studies (GWAS) have the capacity to detect low-risk genetic susceptibility regions associated with prostate cancer with an increased risk varying between 14-52 % (table 3) (Schumacher et al. 2011, Witte 2009). Several recent studies incorporating single nucleotide polymorphism (SNP) analyses in models predicting the diagnosis of prostate cancer upon biopsy have been published (Wiklund 2010, Aly et al. 2011, Witte 2009). Using a genetic model including 35 validated SNPs 23% of prostate biopsies could be avoided at a cost of missing a prostate cancer diagnosis in 3% of patients characterised as having an aggressive disease (Aly et al. 2011). It is hoped that in the future these approaches will reduce the number of negative prostate biopsies being performed, without reducing the detection of clinically significant prostate cancer.

Locus		Allele frequency		Association
Chr Region	SNP	Controls	Cases	Odds ratio
2p15	rs721048	0.19	0.21	1.15
2q37	rs238107965	0.25	0.29	1.14
3p12	rs2660753	0.1	0.12	1.3
6q25	rs9364554	0.29	0.33	1.21
7q21	rs6465657	0.46	0.5	1.19
8q24 (region 1)	rs1447295	0.1	0.14	1.42
8q24 (region 2)	rs16901979	0.04	0.06	1.52
8q24 (region 3)	rs6983267	0.5	0.56	1.25
10q11	rs10993994	0.38	0.46	1.38
10q26	rs4962416	0.27	0.32	1.18
11q13	rs7931342	0.51	0.56	1.21
12q13	rs902774	0.16	0.19	1.17
17q12	rs4430796	0.49	0.55	1.22
17q24	rs1859962	0.46	0.51	1.2
19q13	rs2735839	0.83	0.87	1.37
Xp11	rs5945619	0.36	0.41	1.29

Table 3. Loci associated to prostate cancer and allele frequencies

Results presented for the most significant SNPs ($p<5.10^{8}$) or those reported in multiple studies (Witte 2009, Schumacher et al. 2011).

3. Prediction of prostate cancer aggressiveness

At the time of biopsy most patients will have no clinical evidence of either lymph node involvement or distant metastasis. Patients with clinically localised disease may be offered either a radical treatment or active surveillance, and the choice depends on multiple factors reflected by D'Amico risk groups (table 4) (D'Amico et al. 1999). The assessment of the pathological stage is critical in decisions regarding appropriate treatment options. Patients more likely to have clinically insignificant or indolent prostate cancer may be good candidates for active surveillance whereas those with locally advanced disease may benefit more from a combined treatment options such as radiotherapy and androgen deprivation therapy (Mottet et al. 2011, Heidenreich et al. 2010).

The prediction of indolent prostate cancer was investigated by Kattan et al. based on criteria set by Epstein (Epstein et al. 1994) and defined as organ-confined prostate cancer less than 0.5cm3 with no Gleason grade over 4. The models were based on clinical variables (serum PSA, clinical stage and ultrasound-determined prostate volume) and others derived from the analysis of systematic biopsies of the prostate (Gleason grade, percentage of biopsy cores involved with cancer, presence of high grade cancer and total length of biopsy cores involved). Three models were developed with a c-index ranging from 64% to 79% (Kattan et al. 2003) and these validated on an external cohort resulting in a c-index ranging from 61% to 76% (Steyerberg et al. 2007). These models provide valuable information when counselling patients with prostate cancer who are considering active surveillance.

	PSA	Gleason score	Clinical stage
Low risk (all criteria present)	PSA < 10.0 ng/mL	highest biopsy Gleason score ≤6	clinical stage Tlc or T2a
Intermediate risk (any patient not at high or low risk)	PSA ≥10 but < 20 ng/mL	highest biopsy Gleason score = 7	clinical stage T2b
High risk (any criteria present)	PSA ≥ 20 ng/mL	highest biopsy Gleason score ≥ 8	clinical stage T2c/T3

Table 4. D'Amico et al risk stratification for clinically localized prostate cancer.

The local extension of prostate cancer has been investigated using multiple models. The Partin tables are the most widely used tool to predict the pathological stage of radical prostatectomy specimens based on pre-operative data (Partin et al. 1997), and have been updated many times since their creation in 1993 (Partin et al. 2001, Makarov et al. 2007) in order to correct for the effects of stage migration. The tables predict organ-confined disease, capsular penetration, seminal vesicle infiltration, and pelvic lymph node involvement using PSA level, TNM clinical stage, and Gleason score. They were modified to predict extra-capsular extension, and can assist the surgeon with decisions regarding nerve sparing during surgery (Graefen et al. 2001). This prediction tool was externally validated with a discrimination of 70% (Augustin et al. 2004), whilst the prediction of side of extra-capsular extension was accurately undertaken by Ohori et al. with a c-index ranging between 79%- to 81% (Ohori et al. 2004). Steuber et al. have also validated this prediction tool using an external population resulting in an 84% discrimination figure (Steuber et al. 2006) using the following predictors in a logistic regression model: clinical stage, pre-treatment PSA, biopsy Gleason sum score and percentage of cores positive for cancer in the biopsy specimen.

Other prognostic factors that may be predicted on prostate biopsy include the presence of seminal vesicle involvement (Koh et al. 2003, Gallina et al. 2007) with a c-index of 78% to 88% or lymph node invasion with a discrimination of 76% (Cagiannos et al. 2003, Briganti et al. 2006) Another model may be used to identify with 80% discrimination those patients at risk of lymph node invasion beyond the obturator fossa. This prediction tool may be useful indeciding whether the patients require an extended lymph node dissection (Briganti et al. 2007).

So far, Genome Wide Association Studies (GWAS) have shown little or no ability to discriminate between indolent and fatal forms of prostate cancer and this does not support their use in prediction models as reported by Aly (Aly et al. 2011). It is likely that different genetic components are involved in the initiation rather than the prognosis of prostate cancer and environmental factors may play a stronger role than genetic changes. Ongoing studies exploring the association with disease progression and prognosis rather than stage at diagnosis, will be more effective in detecting genetic risk factors for prostate cancer outcome (Wiklund 2010).

4. Evaluation of prediction tools

Prediction tools are compared using discrimination and calibration. Their use must take into consideration their clinical relevance. This can be investigated by assessing their generalisability and complexity by making adjustments for competing risks.

4.1 Discrimination

Discrimination measures the ability of a predictive tool to discriminate patients according to their outcome, for example the presence of prostate cancer versus benign pathology. Discrimination is measured using a probability score, with the lowest value being 0.5 (i.e. no better than the flip of a coin), and the highest value of 1 representing perfect discrimination (i.e. the prediction tool properly identifying the presence or absence of cancer in all patients). For binary outcomes such as the presence or absence of cancer, the discrimination value is quantified using the area under the curve (AUC). It is also assessed by the c-index for censored data (e.g. the time to biochemical recurrence after treatment) or using the Brier score (Shariat et al. 2009).

Prediction models are usually based on clinical, biological or pathological variables that impact upon the measured end point. Whilst these models are usually more accurate with the inclusion of a greater number of variables, this has to be balanced with the complexity of the model and the need to maintain clinical relevance. The risk of occurrence of the event of interest may change over time. For example the risk of observing biochemical progression at any time after treatment is highest just after treatment, and decreases with the disease free interval. Prediction models therefore need to take these factors into account to ensure accuracy.

4.2 Calibration

Whereas discrimination is an overall measurement of prediction tool accuracy, the term calibration reflects the precision of the test at an individual level. It compares the predicted results for each patient with the observed values. In the case of prostate cancer this may be used to predict the presence of a biochemical recurrence. Calibration is represented using two curves, one being the ideal curve (45 degree slope line) and the other representing the observed test result (figure 1). In an ideal model both curves will overlap. It is useful to identify graphically whether the model is well calibrated for all events or only for some events. It may be accurate for short term prediction of biochemical recurrence, but not for long term prediction of disease outcome (Figure 1). Calibration is usually good when applied to the population used to create the prediction model, but not necessarily to another population in which the clinical variables may differ. It is therefore important that the model is validated on an external population. If the discrimination and calibration are similar it is more likely that the predicting model is robust and therefore generalizable (Shariat et al. 2009).

The blue line represents the result of an ideal prediction model. The red line represents time to biochemical recurrence observed compared with time to biochemical recurrence predicted. Time to recurrence was overestimated at 5 years, and underestimated at 10 years. The curve also shows that the model is more accurate in predicting early than late recurrence.

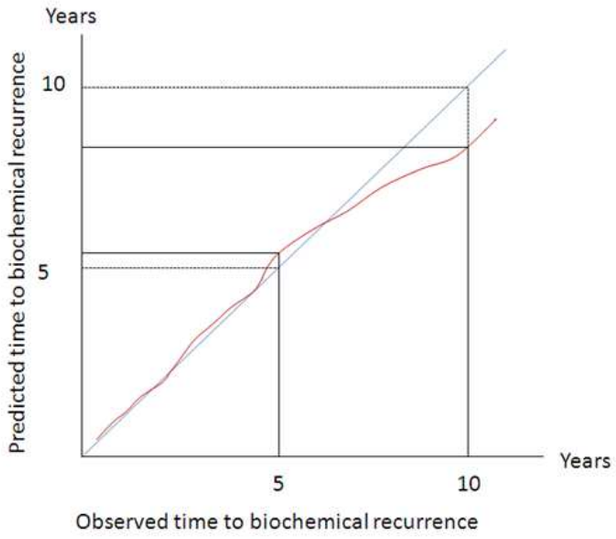

Fig. 1. Example of calibration curve.

4.3 Clinical relevance

4.3.1 Generalizability

The clinical relevance of a prediction tool depends not only on its intrinsic discrimination and calibration performance but also on its generalizability, level of complexity and adjustment for competing risks. It is worth noting that any result applies to the population analysed, and extrapolation to another population should be used with caution. Where a model is more complex and integrates more clinical variables, it is more likely to be generalizable since the model usually adjusts the results according to these variables. Before using a prediction tool prospectively, it is recommended to test the performance of the model on retrospective cohorts. When this approach was applied to populations of patient undergoing radical prostatectomy using the Kattan nomogram (Kattan et al. 1998) the discrimination varied between 0.67–0.83 (Roupret et al. 2009) indicating a poor generalizability. Reduced generalizability may be observed when the stages of cancer at diagnosis are different between populations.

The performance of a predictive tool based on a screened population may differ when used on a non-screened population because the stage at diagnosis tends to be higher in the latter group of patients (Steyerberg et al. 2007). Another common cause of reduced generalizability is the use of models based on a historical cohort of patients treated many years previously. Patient characteristics at diagnosis may have changed over time and new treatments may have impacted on the target point risk. Once again the validation of recent cohorts is necessary unless the prediction model has been modified to take into account the differences observed in more recent cohorts (Greene et al. 2004, Shariat et al. 2009).

4.3.2 Level of complexity

Another parameter impacting on the clinical relevance of prediction tools is the complexity of the model used. Some models are accurate but may require complex algorithms and include large numbers of variables. The use of the model will therefore require computer support and all variables need to be entered manually, which may be time consuming. Some

variables, such as biomarker information, may not be routinely available and the model may not be useful in daily clinical practice. One example is the use of PSA kinetics such as PSA velocity or doubling time which require several measurements, and PSA density, requiring prostate volume information which may not be available routinely (Shariat et al. 2009).

4.3.3 Adjustment for competing risks

Predicting the risk of prostate cancer progression may be irrelevant in the presence of substantial competing comorbidties which could lead to non cancer-specific mortality prior to any progression event. It is therefore of paramount importance to account for competing risks in any predictive model. Adjustment is important when there is a particular risk of over-treatment where intervention can be associated with significant morbidity. (Nielsen et al. 2007).

4.4 Comparison of existing prediction models

When new prediction models are developed they should be compared with existing tools and validated before they are introduced to routine clinical practice. New prediction tests need to be compared to the best current prediction tools using similar populations. These comparisons are best made by assessing discrimination and calibration as highlighted earlier in this chapter, to offer an unbiased and objective assessment of the new model and it is clinical utility. This systematic head-to-head comparison of prediction tools is considered a better approach than a simple comparison of the concordance index or the AUC, although the results may be different depending on the methods used for comparison (Lughezzani et al. 2010).

Comparisons of prediction tests should ideally include a decision analysis to assess the impact of the prediction tool in clinical practice. One of the most simple and efficient methods is a decision curve analysis described previously (Vickers 2008). This method takes into consideration the probability of false positives or false negatives. For example, when considering the prediction of prostate cancer based on a model, a false positive result describes a patient wrongly assigned to have prostate cancer with a negative biopsy result. Conversely a false negative result describes a patient wrongly assigned to not having cancer, who will be denied a prostate biopsy. These false results are given a harm score, with for instance a false negative result for a prostate biopsy with subsequent deleterious delayed treatment. This latter situation is considered four-fold more harmful than a false positive outcome resulting in an unnecessary prostate biopsy. Clinical consequences of the different models can therefore also be compared in terms of the potential harm they may cause. Such analysis is best performed during the late stages of model development before the tool is implemented clinically (Lughezzani et al. 2010).

4.5 Prediction tools of the future

Many of the current prostate cancer prediction tools are imperfect, lack discrimination and are often difficult to use in daily clinical practice. The addition of other potentially informative clinical and pathological data has not resulted in significant improvement of current models. Nevertheless further improvement of existing models is potentially possible by implementing imaging data, use of biomarkers, and the use of "smart" electronic medical records.

Non-invasive imaging in the field of prostate cancer diagnosis, staging and treatment planning has gained widespread acceptance in recent years. Magnetic resonance imaging (MRI) data has been implemented in several prediction tools in order to accurately identify

organ-confined prostate cancer (Wang et al. 2007) or to detect clinically relevant disease (Shukla-Dave et al. 2007), however to date this has not been properly investigated in the diagnosis of prostate cancer before biopsy.

Over the past few years numerous reports identified promising new biomarkers associated with the presence of prostate cancer which correlate with its aggressive behaviour (Reed and Parekh 2010, Shappell 2008). The introduction of urine and blood biomarkers in predictions tools was investigated to predict more accurately disease relapse after radical prostatectomy (Shariat et al. 2008a, Shariat et al. 2008b). Clinical practice is currently based on the interpretation of a handful of parameters by physicians without automated support, but it has been demonstrated that prediction models may perform better than the clinician regardless of their levels of expertise (Ross et al. 2002, Walz et al. 2007). Improvements in technology now make it possible to assess rapidly large amounts of molecular biology data at a greatly reduced cost compared to the recent past. The use of computational algorithms to analyse the results of biomarker tests, and the use of evidence-based data to support this approach, is likely to improve patient care but this has not yet been confirmed.

In the future, these algorithms may be incorporated into "smart" electronic medical records with the ability to analyse a patient's individual risk of harbouring clinically significant disease, using new and conventional clinico-pathological data such as pathology results which will need to be reported as specific fields (e.g. primary and secondary Gleason scores) as well as in the conventional manner as a text result. This approach requires modifications of clinical practice with the wide implementation of electronic medical records. Algorithms could then be refined by merging data from multiple centres with different patient populations, and the integration of other investigations such as multiparametric MRI scanning.

5. Conclusion

Currently, many parameters can be used to estimate an individual's risk of harbouring prostate cancer on biopsy. Pre- and post-biopsy factors require further investigation to determine whether the cancer detected is potentially aggressive. This is critical to predict whether a prostate biopsy is likely to offer real benefit to individual patients, and to guide therapeutic options. Despite the multiple limitations described above, predictive tools could, in the future provide personalised and evidenced based information, including molecular tumour profiling of individual patients to improve the outcome of such a common and ubiquitous disease as prostate cancer.

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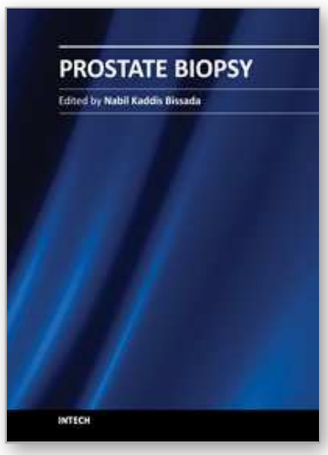

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Prostate Biopsy represents the standard procedure for diagnosing Prostate Cancer. This procedure can be performed transrectally, through perineum or occasionally through the urethra. Although the procedures of Prostate Biopsy are covered in numerous publications, there is still a need for gathering different aspects and methods in one source. Hopefully, this book will help physicians in their effort to provide the best treatment for their patients.

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