Prostate Cancer Treatment on the Basis of an Individual Risk Profile; Can we Reduce Overtreatment?

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Abstract: Prostate cancer (PCa) is the most prevalent cancer in male population with an incidence rate of 93 per 100.000 men in Europe and is the sixth leading cause of cancer related deaths in men. In the last two decades the incidence of PCa has increased, which is related to widespread prostate-specific antigen (PSA) based screening and increased life expectancy. Mortality rates of prostate cancer have been reduced due to improvement in treatment and/or the widespread screening activities. Major down sides of screening are the potential risks of overdiagnosis and subsequent overtreatment. Approximately 50% of PCa cases detected through screening are potentially overdiagnosed and hence do not require active treatment. However, in clinical practice men with a potentially non-life-threatening cancer (indolent cancer) are often treated actively resulting in unnecessary suffering from serious side effects coinciding with active treatment. The way out of this dilemma is two-fold. First, the actual diagnosis could be delayed or even avoided and second, radical treatment could be delayed or avoided for patients with low-risk PCa. To better predict the presence of a (potentially indolent) prostate cancer nomograms have been developed. These multivariate prediction tools can be of aid in avoiding unnecessary biopsies reducing overdiagnosis, or identifying potentially indolent prostate cancer after diagnosis and hence adapt the treatment strategy. In this expert opinion we discuss the available tools and their performance in reducing the unwanted side effects of prostate cancer screening. In addition, we provide an overview of strategies concerning optimisation and individualisation of treatment, to reduce overtreatment of prostate cancer.

Keywords: Prostate cancer, indolent disease, PSA, screening, mortality reduction, overdiagnosis, overtreatment, comorbidity, prediction tool, nomogram, risk calculator.

INTRODUCTION

Prostate cancer (PCa) is a major health problem. It is the most prevalent cancer in male population. The last two decades incidence rates have increased rapidly. With an incidence rate of 93 per 100.000 men in Europe it is the sixth leading cause of cancer related deaths in men [1]. The increased incidence of PCa is related to widespread prostate-specific antigen (PSA) based screening, increased awareness of PCa and increased life expectancy [2]. In 2008 over 258.000 deaths were related to PCa globally [1].

The suspicion of the presence on PCa is based on several tests. In general a digital rectal examination (DRE), transrectal ultrasound (TRUS) and serum prostate specific antigen (PSA) testing are used to decide whether a prostate biopsy is indicated. At the moment the ultrasound guided prostate biopsy is still considered the “gold standard” in the diagnosis of PCa. Previously, often in response to an abnormal DRE a biopsy was performed; today PSA determination is usually the cause.

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Due to the increased screening of PCa in the current PSA era the incidence of the disease has almost doubled in the last twenty years [2]. Mortality rates of PCa are declining most likely due to improvement in treatment and/or the widespread screening activities [3, 39]. The European Randomised Study for Screening of Prostate Cancer (ERSPC) concluded that systematic PSA-based screening for prostate cancer of the general population reduces prostate cancer specific mortality by at least 20% [4]. The Goteborg trial (part of ERSPC) showed that prostate cancer mortality was reduced by almost 50%, applying a two year screening interval and having the availability of 14 years of follow-up [5].

Major down sides of screening are the potential risks of overdiagnosis and subsequent overtreatment [4, 5]. As PSA screening increases, more patients without any clinical symptoms are diagnosed with PCa, which possibly would never become clinically apparent [2]. It is estimated that approximately 50% of PCa cases detected through screening are potentially overdiagnosed and hence do not require active treatment [2]. However in clinical practice men with a potentially non-life threatening cancer (indolent cancer) are often treated actively resulting in unnecessary suffering from serious side effects coinciding with active treatment. Over 90% of men with PSA-detected prostate cancer undergo early treatment and less than

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7% elect for active surveillance in the United States [6]. The introduction of PSA screening has resulted in the United States in more than 1 million additional men being diagnosed and treated [7]. Active treatment options are associated with adverse outcomes; after prostatectomy or external radiotherapy, erectile dysfunction and urinary incontinence may occur. Urinary incontinence was observed in 14% and 31% after surgery and in 4% and 13% after radiotherapy; erectile dysfunction was observed in 79% and 88% after surgery and in 63% and 64% after radiotherapy [8, 9]. Maintaining quality of life after active treatment is an important issue. A Scandinavian randomized trial compared radical prostatectomy to watchful waiting and showed no difference in any psychological domain between the watchful waiting and surgery group [10]. Quality of life data showed that negative side effects of both strategies were common and that both interventions added more stress than would be seen in a background population. In the prostatectomy group, urinary leakage and erectile dysfunction were often consequences of surgery, whereas in the watchful-waiting group, they were due to tumor progression and/or hormone treatment. Most side effects concerning the urinary tract improved after some years, but substantial symptoms persisted in many patients up to 5 years after treatment. They reported lower physical functioning 5 to 10 years after treatment than the control group of similar age [10]. In a study using a computer model as a virtual laboratory for translational research based on the results from one of the leading active surveillance cohorts, the authors concluded that active surveillance among men diagnosed with low-risk prostate cancer could lead to significant benefits in terms of quality of life comparing to men treated with immediate radical prostatectomy [45].

Additional methods are desirable to identify men with a potentially life threatening cancer or vice versa to identify those without a potentially life threatening cancer. This will decrease the adverse effects of screening. The way out of this dilemma is two-fold. First the actual diagnosis could be delayed or even avoided and second, radical treatment could be delayed or avoided for patients with low-risk PCa.

In this expert opinion we discuss the available prediction tools and their performance in reducing unwanted prostate biopsies and overdiagnosis. In addition, we provide an overview of strategies concerning optimisation and individualisation of treatment, to reduce overtreatment of prostate cancer.

PREDICTION TOOLS; REDUCING BIOPSIES AND OVERDIAGNOSIS

To better predict the presence or outcome of disease, prediction tools have been developed. They are being used increasingly in modern medicine [14]. A recent literature review identified >100 predicting models for prostate cancer outcome [11, 12]. These multivariate prediction models and nomograms may be helpful in shared-decision making [13]; they can be of aid in avoiding unnecessary biopsies resulting in the diagnosis of a potentially indolent cancer or to identify potentially indolent prostate cancer after diagnosis and hence adapt the treatment strategy. The current tests (DRE, TRUS and serum-PSA) for predicting the presence of PCa in an individual patient, have their specific weaknesses and strengths. Other risk factors can be helpful, such as family history, age, prostate volume and prior negative biopsies. Combining tests might help to increase the predictive capability. By including all these factors into a prediction model the likelihood of a biopsy detectable (potentially aggressive) PCa can be assessed which can be helpful in the question whether or not to perform a prostate biopsy [11].

The reason for this consideration is that a prostate biopsy is not a harmless procedure, minor side effects are more common than major side effects; haematuria and haemospermia occur in 22.6% and 50.4% of men biopsied, respectively [42]. Major side effects were studied in a large European screening cohort; fever and hospital admission were reported in 4.2% and 0.8%, respectively. Although most fevers were managed on an outpatient basis, 81% of hospital admissions were for infection [43].

In addition, to simply predict biopsy outcome (having PCa yes or no) some risk calculators may help us discriminate potentially low risk cancer from aggressive cancer and estimate the risk of progression. Hence these different predicting tools exist throughout the path from screening to palliative treatment.

TOOLS PREDICTING BIOPSY OUTCOME

There are three commonly known online risk calculators predicting the presence of a biopsy detectable PCa. The North-American Prostate Cancer Prevention Trial (PCPT) risk calculator [15] is based on a study evaluating a possible preventive effect of Finasteride in PCa development and includes serum-PSA, outcome of DRE, prior biopsy, race, age and family history. Data was obtained from over 5500

males from the placebo group and these were used to create the risk calculator. There was a reported AUC of 0.70 for the calculator in the original study, which was higher than the 0.68 reported for PSA alone [16]. It has been validated in external populations, with accuracies ranging from 0.57 to 0.74 [17-19].

The second is the Sunnybrook risk calculator which combines a variety of variables like DRE, PSA, percent free PSA, age, ethnicity, family history of PCa and urinary voiding symptom score [20]. It is derived using a clinical cohort of 3100 men. It achieved an AUC of 0.74 for any PCa and 0.77 for high-grade cancer. This was significantly greater than the conventional screening method of DRE and PSA only, which was 0.62 for any cancer and 0.69 for high-grade cancer [21]. As was demonstrated in a prospective head-to-head comparison in more than 2100 patients who underwent a prostate biopsy, the Sunnybrook calculator outperformed the PCPT model (AUC 0.67 vs. 0.61 for any cancer; 0.72 vs. 0.67 for predicting aggressive disease) [22]. However, decision curve analysis demonstrated that neither calculator was of clinical benefit, because it did not show a probability threshold considered acceptable with respect to saving biopsies and missing PCa [22].

The third risk calculator is from the European Randomized Study of Screening for Prostate Cancer (ERSPC), which has developed its own online prediction models based on data from the Rotterdam cohort consisting of 6200 Dutch males randomised to the screening arm and aged 55-74 years at time of screening in ERSPC [23, 25]. The risk calculator contains six different steps. According to age, PSA, family history, LUTS, DRE, prostate volume, transrectal ultrasound (presence or absence of hypoechogenic lesions) and prior biopsy information the chance of a negative of positive biopsy and an indolent or aggressive PCa can be calculated. Step 1 and 2 are meant for lay men and GP's and use readily available information (age, LUTS, family history and PSA) to calculate a rough estimate on the chance of having a biopsy detectable PC. Step 3 estimates the chance of a positive prostate biopsy in previously unscreened men and step 4 in previously screened and (optionally) biopsied men using additional information from the outcome of PSA, DRE and TRUS [24, 25]. A promising tool for reducing overdiagnosis of PCa is a fifth risk calculator which has been developed to predict potentially indolent PCa using PSA, TRUS assessed prostate volume and biopsy information; namely Gleason score and tumor involvement [26]. Screening on the basis of an individual risk assessment using these risk calculators can result in a considerable reduction of unnecessary biopsies and only few important PCa cases (for which diagnosis at a subsequent screening visit might be too late for treatment with curative intent) would be missed [24]. Applying risk calculator 5 and using a cut-off of >70% probability of having a potentially indolent PCa for the practice of a conservative form of treatment (active surveillance), about 6% of non-indolent tumours are going to be considered as indolent, and only until they are recognised as a significant tumour, they will be treated as indolent cancers [26]. Step 6 is the latest in the series of prediction tools; it calculates the risk of PCa 4 years after an initially negative screen. It is based on age, PSA, DRE, family history, prostate volume, and previous biopsy status [44]. It predicts an individual's 4-year risk of developing the disease and facilitates stratification of risk, predicting the chance on low- and high-risk PCa, and as such can be of aid in planning future PSA test and/or re-biopsy.

In a head-to-head comparison of the ERSPC and PCPT online nomograms for prostate biopsy outcome prediction, the accuracy of these risk calculators was compared in a specific Portuguese population. Both tools were confirmed to be superior to PSA alone. The ERSPC displayed a 7.96% increase in the predictive accuracy compared to the PCPT (77.9% vs. 69.9% respectively) (p=0.002) [27]. In two other head-to-head comparisons, the ERSPC risk calculator again outperformed the PCPT model [28, 29]. The ERSPC risk calculator (AUC: 0.71) was superior to the PCPT model (AUC: 0.63) and PSA (AUC: 0.55), which was showed after validation in referred patients from a North American cohort [29]. In addition, the ERSPC calculator has been validated in the Finnish and Swedish cohort of the ERSPC [30]. It discriminated well between men with and without PCa among initially screened men, but overestimated the risk of a positive biopsy. External validation of the PCPT calculator across 10 international cohorts revealed varying degree of success highly dependent on the cohort, most likely due to different criteria for and work-up before biopsy; AUCs ranged from a low of 56% to a high of 72% in the ERSPC cohorts and were statistically significantly higher than that of PSA in 6 out of the 10 cohorts [46]. There was limited to no net benefit to using the PCPT calculator for biopsy referral compared to biopsying all or no men in all five ERSPC cohorts and benefit within a limited range of risk thresholds in all other cohorts [46].

The external validity of the ERSPC risk calculator was assessed in a contemporary clinical cohort. This prospective validation in 320 biopsied Dutch men, with no previous prostate biopsy, showed that the calculator predicted a positive biopsy better than a model with only PSA and digital rectal examination, AUC 0.77 and 0.71, respectively [47].

In contrast to validations, compliance studies are rarely performed. A study among 443 patients showed that compliance of both patients and urologists with the ERSPC risk calculator recommendation was 83%; in 96% of cases with biopsy recommendation, patients complied, while 36% of patients with a negative biopsy advice were actually biopsied [48].

A recent paper proposes a new standard for prostate cancer testing, on the basis of risk-adjusted screening guidelines, with the aim of defining those subgroups of men that most stand to benefit from prostate cancer screening [55].

In summary, in men with a known PSA, risk calculators may hold the promise to identify those who are at increased risk of having PCa and are therefore candidates for biopsy. The risk calculators described above have been validated in external populations and screening cohorts with varying results. Active implementation into daily clinical practice shows encouraging results, although currently no empirical data exists. Further research in this field including long term follow-up is needed.

ACTIVE SURVEILLANCE; STRATEGIES TO AVOID OVERTREATMENT

Active surveillance (AS) is a strategy that aims to individualise therapy by selecting only those men with significant cancers for curative therapy. It consists of actively monitoring the disease according to a protocol with PSA tests, DRE and prostate (re-)biopsies [35]. The most commonly used criteria for AS are prostate-specific antigen ≤10.0 ng/ml, PSA-density <0.2 ng/ml per ml, stage T1C/T2, Gleason score ≤3+3=6, and ≤2 positive biopsy cores [49]. Patients with favourable tumour characteristics are closely monitored using PSA tests and repeat prostate biopsies. The choice between continued observation and radical treatment is based on disease progression, often defined in terms of the PSA doubling time and/or “upgrading” at repeat biopsy [49]. The aim of active surveillance is to postpone or even avoid invasive therapy, like radical prostatectomy or external radiotherapy in men with low risk disease. Invasive therapy is indicated, when the tumour shows progression during monitoring [36].

AS has become a widely accepted management strategy, especially for older men with low grade PCa and low volume disease [31]. A retrospective study in which outcome measures in men with screen-detected PCa that fit the prementioned criteria and who were managed expectantly, showed a favourable PCa specific prognosis, after 10 years of follow-up, no PCa specific mortality was reported, whereas 23% already has died of other causes [50]. Clinical results of long-term follow-up in large prospective active surveillance cohorts show low rates of prostate cancer mortality, up to 10-year PCa-specific survival rates approaching 98% [32-34]. Men that have been in an Active Surveillance program showed that metastases were diagnosed in 1 of 200 men at the time of the shift towards invasive therapy [41].

Because non-invasive monitoring based on PSA testing of men with PCa entail the risk of disease progression, repeat transrectal biopsies are the cornerstone of AS [37, 38]. In a large AS cohort of 757 patients the first repeat biopsy was taken after a median follow-up of 1 year, which led to reclassification of risk in 21% of patients [40]. However these data should be interpreted with caution since there may have been potential understaging at time of the diagnostic prostate biopsy.

The currently applied inclusion criteria for AS thus may select men with significant disease. Applying a probabilistic selection using a nomogram which includes the clinical parameters lika PSA, T-stage and Gleason score might be of help and may decrease the frequency of misclassification. This was studied within ERSPC using men with screen detected PCa and having had a radical prostatectomy (n=1011). With indolent PCa defined as a tumour volume less than 0.5 cc, and confined to the prostate, and with no Gleason pattern 4 or 5, a total of 26% of men had an indolent PCa. Stricter rule-based and higher thresholds criteria (i.e. a PSAD threshold of <0.15 ng/ml/cc and <0.10 ng/ml/cc instead of <0.20 ng/ml/cc, a maximum number of positive biopsy cores of 1 instead of 2, and a maximum percentage of biopsy core tumour involvement of 50% instead of no threshold) of indolent disease resulted in a higher frequency of indolent disease that was included for radical prostatectomy, up to 61-67%, but at the cost of a decrease in the number of men suitable for AS, down to 2-17%. These

refinements in selection did not have a significant effect on biochemical progression rates [data coming from ERSPC, oral communication, thesis from R. van den Bergh, 2009, ISBN: 978-90-8559-602-8].

Although Active Surveillance appears to be a safe treatment option, longer follow-up of patients with favourable PCa risk profiles is desirable, to optimise and balance the inclusion criteria and criteria to switch to active treatment. One of the largest prospective Active Surveillance studies designed to evaluate these issues is the PRIAS study; a follow-up registry for active surveillance of low-risk prostate cancer, initiated in 2006 [53]. Recent data from the PRIAS study combined with an overview of the literature from the past 3 years showed that risk reclassification on repeat biopsy has occurred in 27% of men and a switch towards active therapy occurred in 22% of men under AS [53].

As mentioned earlier, compliance studies on nomogram recommendations have been rarely performed. In one of the first studies to investigate the compliance of urologists and patients with recommendations concerning the probability of indolent PCa based on a risk calculator, and hence treatment choice data showed that AS and active treatment recommendations were followed by 82% and 71% of patients, respectively [54]. However 29% with active treatment recommendations (based on a calculated probability of indolent disease < 70%) chose AS instead. The most common reason for non-compliance with active treatment recommendations by urologists was the patient's preference for AS. The threshold set for a recommendation of AS vs. active treatment may be too high for urologists and patients, however the risk calculator proved to be useful for patients in decision-making, because AS recommendations were followed by most patients [54].

TREATMENT WITH AS, SWITCHING TO ACTIVE TREATMENT

PSA kinetics are generally assumed to be indicative of tumor progression and are therefore used in decision-making in men on AS for PCa. A review showed that the evidence concerning the prognostic value of the PSA doubling time (PSA-DT) is sparse, especially in active surveillance, and therefore should be combined with other diagnostic measures as the trigger for repeat prostate biopsies or radical treatment [51]. Therefore nomograms are currently based on Gleason scores, PSA-level kinetics and DRE. In the near future, advanced radiologic imaging and new biologic markers, should help clinicians and patients choose optimal follow-up and treatment pathways. The improvement of non-invasive biomarkers in serum or urine, or radiologic interventions like MRI-guided prostate biopsies to monitor disease progression can possibly alter current AS schemes. The use of genetic markers, such as PCA3 and TMPRSS2-ERG, has the potential to aid disease screening and improve prognostic discrimination [52]. A recent literature review revealed however that most markers have not yet been prospectively validated for providing useful prognostic or predictive information. In the future these clinically diagnostic tests may improve clinical decision making [52].

Besides the currently available static models which include patient and tumor characteristics at baseline, prognostic models should take new information into account that accumulate during follow-up which change the clinical status of the patient. This so-called dynamic risk modelling allows updating the prognosis of a patient according to the evolution of his disease. Updated predictions will allow individualized management of the patients follow-up schemes and enable tailored choices concerning different treatment modalities. Further research should therefore focus on the development of these dynamic models including potential new biomarkers in order to reach an optimal outcome of survival and quality of life.

CONCLUSION

Systematic PSA-based screening can reduce mortality from PCa. However, currently it coincides with considerable harms, such as unnecessary testing and prostate biopsies and overdiagnosis. With risk stratification tools, we may be able to identify these men who are at increased risk of having a potentially life threatening PCa, and therefore avoid biopsies in men who are not likely to benefit from it. In addition, in men with low risk disease, active surveillance, including dynamic risk stratification at time of inclusion and during follow-up can be considered a management strategy to postpone or even avoid radical treatment, although currently no empirical data exists.

To reduce overdiagnosis and overtreatment of prostate cancer in the current PSA era, individualization and optimization of diagnosis, monitoring and treatment thus is desirable in which nomograms are likely to play an important role.

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