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TOPIC PAPER

Algorithms, nomograms and the detection of indolent prostate cancer

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Abstract

Purpose   Prostate cancer is the most commonly diagnosed cancer in men. However, only about 12% of the men diagnosed with prostate cancer will die of their disease.
Result   The serum PSA test can detect prostate cancers early, but using a PSA based cut-off indication for prostate biopsy results in unnecessary testing in app. 75–80% of the men and perhaps even more important the serum PSA test cannot tell how aggressive the cancer is. To decrease unnecessary testing different test results are often combined, converted into a probability and displayed graphically. There are more than 40 of these so called nomograms in the case of prostate cancer. These nomograms can be divided into two categories, namely those that predict biopsy outcome using results from serum determination(s) or non-invasive tests such as the DRE and TRUS. The second category represents those nomograms that predict tumor characteristics and prognosis using information coming from pathology review.
Conclusion   The ultimate nomogram able to predict tumor characteristics and progression purely based on non-invasive testing will for a large part put an end to the negative side effects and uncertainties that coincide with the early detection of prostate cancer, if it will ever be made.

Keywords   Prostate · Early detection ·
Indolent · Nomogram · PSA

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Introduction

Prostate cancer is the most commonly diagnosed cancer in men. However, only about 12% of the men diagnosed with prostate cancer will die of their disease [1]. Already since the early nineties there have been two mainstreams of thinking about the early detection of prostate cancer using the serum PSA test. One extreme is represented by those who are definitely against screening for prostate cancer and consider it as unwarranted [2, 3]; the opposite view is represented by those investigators who argue that men should not be denied the opportunity of early detection and treatment [4, 5].

In the past 15 years no consensus has emerged and prostate cancer screening is still a controversial issue [6–12], resulting in very different screening policies in different countries, varying from very aggressive screening algorithms, where men are screened every 6 to 12 months starting as early as the age of 40, to no screening at all [13–18].

Several studies have been undertaken to determine the validity of mass screening [19–22]. The only scientifically valid way to determine whether early detection indeed has an effect on prostate cancer mortality is a randomized controlled trial with prostate cancer death as main endpoint. Two large trials are ongoing namely the European Randomised Study of Screening for Prostate Cancer (ERSPC) [23] and the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial [24] and an answer can be expected within the next three years.

Population based screening for prostate cancer has not been adopted in most health care systems due to this uncertainty regarding its efficacy in decreasing prostate cancer specific mortality at an acceptable effect on quality of life and cost. In a population based setting, where many

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participants and considerable amounts of money are involved, specificity is a crucial issue.

So apart from the lack of evidence that early detection of prostate cancer will indeed reduce prostate cancer mortality the differences of opinion about prostate cancer screening are mainly based on several issues relating to specificity. The first is the lack of a screening test or combination of tests that can efficiently identify men with an elevated risk of having prostate cancer in an asymptomatic population in order to avoid unnecessary invasive testing. Next to this it is not clear yet which men should actually be tested (age cut-off? high risk men? repeat biopsies?) and what should be the optimal time period between subsequent screenings. Finally there is the lack of knowledge about which prostate cancers are life threatening, and need to be detected, and which are not.

The concept of early detection and as a result offering a better chance of cure and reducing prostate cancer specific mortality seems to speak for itself and sounds convincing. But some prostate cancers develop so slowly that they would likely never cause problems.

The serum PSA test can detect prostate cancers early, but it cannot tell how aggressive the cancer is. Simply because an elevated PSA level, some men will be diagnosed with a prostate cancer that would never have caused any symptoms or lead to their death. They may however still be treated with either surgery or radiation, either because the uncertainty of the urologist on the aggressiveness of the cancer, or simply because the men are uncomfortable not having any treatment. These treatments can have side effects that seriously affect a man's quality of life. The decision on who should receive treatment and who might be able to be followed without being treated right away (active surveillance) is one of the top priorities in prostate cancer research at the moment [25–27] awaiting the optimal approach for the early detection of prostate cancer; a non-invasive screening test which should be able to predict the presence of a life threatening prostate cancer.

Screening tests

For a screening test to be useful, certain conditions must be met: firstly the screening test must be valid. The validity is measured by its ability to distinguish between subjects with the condition and those without. The validity of a screening test is determined by its sensitivity and specificity. These vary with the screening test, not the population. A good screening test preferably will have a high sensitivity and specificity and must be rapid, simple and ideally non-invasive and acceptable for the population screened. Sensitivity is defined as the proportion of men with a positive test result of those who truly have the disease. Specificity is defined as the proportion of men with a negative test result of those patients who are known to be free of the disease. Also to be considered in the evaluation of a screening test is the positive predictive value (PPV), which reflects the possibility that if the test is positive, the patient has the disease in question. To calculate the true sensitivity the underlying prevalence of the disease should be known. This is not the case for prostate cancer. Therefore, sensitivity is almost always based on the number of positive biopsies in the screened population as a "gold standard". Sensitivity defined in this way is termed "relative sensitivity". Next to the sensitivity of a screening test the specificity is of great importance in a population based screening program, simply because all those with a positive screening test(s) need further workup (i.e. prostate biopsy), which may cause unnecessary damage, mental stress and costs.

In prostate cancer screening there are basically three tests that serve as indicators for the need of further testing, i.e. the digital rectal examination (DRE), transrectal ultrasonography (TRUS and the derived prostate volume) and most important, the serum prostate specific antigen (PSA) level and its sub forms. Each individual screening test has its plusses and minuses and often test results are combined in order to get a more accurate prediction on the presence of prostate cancer yes or no.

The combinations of test results that are converted into a probability and displayed graphically are called nomograms. In the case of prostate cancer more than 40 nomograms have been published indicating the uncertainty in the detection and management of prostate cancer that still exist [28].

Nomograms can be seen as a physician with data of hundreds or even thousands of patients stored inside his brain, but without the human biases such as wishful thinking and last case syndrome. The different nomograms have been developed for all steps during the path from the risk of having a biopsy detectable prostate cancer to survival after the development of metastatic disease.

Screening algorithms and nomograms for the detection of prostate cancer

The use of nomograms in the decision to perform a PSA test or a prostate biopsy for the actual diagnosis of prostate cancer is not standard practice. This is mainly caused by the fact that most national guidelines do not recommend PSA testing, however it is commonly known that opportunistic PSA testing is common practice [29–33].

Several studies have been performed to assess the reasons why physicians order a PSA test or why men want to have a PSA test [34–37].

Often the PSA test is seen as just another blood test and that any testing for cancer is so-called "responsible health behavior". Wives, friends and the media often trigger requests for PSA testing. Next to this there is a lack of communication about the uncertainty that is present in both the test and treatment options. Discussions between physician and patient on the pro's and con's of prostate cancer screening therefore sometimes do not occur.

A first attempt to objectively help a man in the decision to have a PSA test yes or no is made with the development of the risk indicator® based on the screening results of men participating in the Dutch part of the European Randomised study of Screening for Prostate Cancer (ERSPC: http://www.uroweb.org).

After the result of a PSA test is known the next question is whether this test should be repeated and if so when or whether a prostate biopsy is indicated or can be delayed or is not necessary at all. Several studies have addressed this issue and the general agreement is that rescreening intervals should be related to the serum PSA level [38–40]. Intensively screening in men with low PSA levels (i.e. <3.0 ng/ml) will detect potentially life threatening cancers [41] but at the same time has the great disadvantage of unnecessary testing and overdiagnosis and subsequent overtreatment of considerable more potentially indolent prostate cancers [42, 43]. Next to this it is shown that shortening of the screening interval does not automatically lead to less (aggressive) interval cases (prostate cancer diagnosed during the screening interval but not by screening) [44].

Up to now the decision to actually perform a prostate biopsy is almost always based on a serum PSA level cut-off value, sometimes in combination with the results of the digital rectal examination (DRE) and/or derivates of the serum PSA level (free PSA, free/total PSA ratio).

The most commonly used cut-off values are 3.0 or 4.0 ng/ml which result in referral of app. 20–25% on asymptomatic men in the age range 55–74 years.

There are however numerous studies that report on the possible help of a nomogram.

These nomograms are predictive models that combine available relevant pre-biopsy information into a probability score, almost all claim a considerable decrease in the number of unnecessary biopsies depending on the probability cut-off used [45–49].

Readily available on line nomograms are the earlier mentioned risk indicator® of ERSPC and the riskcalculator of the prostate cancer prevention Trial (PCPT) (http://www.compass.fhcrc.org/edrnnci/bin/calculator/).

The latest development in predicting biopsy outcome in order to decrease the number of unnecessary biopsies is the use of a urinary assay for PCA3. PCA3 turns out to be independent of prostate volume, serum PSA level and the number of prior negative biopsies and could be incorporated into a nomogram for improved prediction of biopsy outcome [50].

Empiric data on the results of nomogram based screening for prostate cancer are not yet available. Although results coming from the prostate arm of the Prostate Lung Colorectal and Ovarian cancer screening trial (PLCO) and its comparison with the purely PSA based screening results of the Dutch part of ERSPC can give some insight in the value of additional pre-biopsy information in the decision to perform a biopsy [51, 52]. Within the PLCO algorithm there is an additional step after PSA determination and before taking a prostate biopsy. Participants with an elevated PSA level or an abnormal DRE are advised to see their primary care provider for diagnostic follow-up. He or she used clinical judgment knowing other available information such as previous PSA levels, prostate volume, family history and previous negative biopsies in determining who should get biopsied. This additional step resulted in a 38–40% higher PPV of the prostate biopsy depending on the PSA level at the time of biopsy.

Algorithms and nomograms for the management of prostate cancer

After the diagnosis of prostate cancer is made the urologist and patient are often confronted with yet another dilemma. Radical prostatectomy, external beam radiotherapy, brachytherapy or active surveillance are all potential treatment options for patients with a clinically localized prostate cancer.

Choosing a therapy however does not only involve cure or the avoidance/delay of metastases but co morbidity and quality of life issues play an important role. Therefore individual information on treatment success, complications and related morbidity are essential in treatment decision making for both urologist and patient. Since nomograms incorporate all relevant predictive factors available at individual level they can provide very valuable information in the decision process.

Although no surveys have been published that assess the actual use of the nomograms available it is known from a small survey done by ASCO in 2004 that the prostate cancer nomograms were the most common disease-specific Palm applications among the Oncologists (personal communication M Kattan).

Probably the best known prediction tool that helps with treatment choice are the so-called Partin tables that using clinical stage, biopsy Gleason score and pretreatment PSA level to predict the pathological stage of the radical prostatectomy specimen [53].

Several other nomograms have been developed that estimate the likelihood of progression when choosing a certain

therapy. For example Kattan et al. developed pretreatment nomograms that predict the probability to remain free from disease progression when choosing a radical prostatectomy [54], external beam radiotherapy [55] and brachytherapy [56].

Combining nomograms: the ultimate goal

After an initial period of optimism caused by the stage and grade reduction at time of diagnosis as a result of the introduction and application of the PSA test as a screening tool doubts have arisen about PSA based screening. The question arose whether all these low stage and low grade prostate cancers should have been detected since they most probably never would have surfaced clinically and thus never would have caused any problems or would have become life threatening. Nowadays low-risk or indolent prostate cancer constitutes up to 50–60% of all newly diagnosed prostate cancers [1]. These insights triggered researchers to develop nomograms that could predict the chance on whether the cancer detected will lead to prostate cancer death [57] or the likelihood of having an indolent prostate cancer. Important to note is the fact that these prediction tools require information coming from prostate tissue thus can only be used after performing a prostate biopsy.

An indolent prostate cancer that is defined as a cancer that does not need immediate invasive treatment but can be monitored and treated curatively if progression should occur. With doing so unnecessary invasive treatment can be prevented in those men that will die of other causes than their prostate cancer.

Kattan et al. [58] developed a nomogram to predict indolent disease based on clinically detected prostate cancers, which was later on adapted to a screening setting by Steyerberg et al. [59]. Basis for the calculations were prostate cancer cases with favorable characteristics such as a T1C or T2A clinical stage, No Gleason pattern 4 or higher, 50% or less positive cores and PSA at time of diagnosis less than 20 ng/ml.

Important difference between the two cohorts under study was the percentage of men with high probabilities of having an indolent prostate cancer within the strict inclusion criteria. Within the screen detected cohort a third of the men had predictions of 60% or higher while in the clinical setting only a few cases had these high predictive probabilities of having an indolent prostate cancer.

Together with the nomogram for prediction of indolent prostate cancer in a screening setting suggestions for treatment in combination with probability cut-off values are given. Conservative management may be appropriate in patients with a high probability of indolent cancer, e.g.

exceeding 60%. In those with a low probability, e.g. less than 30%, potentially curative management may possibly be advised. This nomogram is also incorporated in the risk indicator® and was applied to the prostate cancer cases detected at initial and repeat screening within the ERSPC section Rotterdam. It turned out that 17% of the prostate cancer cases detected at initial screening and 45% of the cases detected at repeat screening 4 years later had a probability of being indolent of more than 60%. This means that within a PSA based screening setting a substantial percentage of the cancers detected can be identified as potentially indolent and can therefore be considered for active surveillance [60].

Being a relatively new treatment option for prostate cancer the guidelines for active surveillance are not quite clear yet. Uncertainties currently exist concerning the risk of missing the window of curability and criteria to rely of for changing from active surveillance to curative therapy in time [61].

One of the initiatives to gain more insight into these uncertainties is the initiation by the department of Urology of the Erasmus Medical Center in Rotterdam of the web based prospective PRIAS trial (Prostate cancer Research International: Active Surveillance, http://www.prias-project.org) [62].

Other ongoing studies on the value of active surveillance for potentially indolent prostate cancer are the prospective cohort of Klotz [63] in Canada and at the Royal Marsden Hospital in the UK [64].

However both the individualization of the screening algorithm with the possible use of nomograms and the application of active surveillance for those prostate cancers that most probably are over diagnosed are in fact temporary measurements that do not solve the actual problem in prostate cancer screening namely not being able to identify life threatening prostate cancer before invasive testing such as a prostate biopsy is performed.

Passing this final hurdle would require a combination of the available nomograms on predicting biopsy outcome (mostly based on laboratory measurements and non-invasive tests) and the nomograms on predicting the presence of a life threatening or indolent prostate cancer (up to now only based on pathological data coming from prostate biopsy or even radical prostatectomy specimens).

A first attempt to assess the effect of a nomogram based biopsy indication instead of a PSA cut-off based biopsy indication in combination with the characteristics of cancers that would have been detected or missed was done with applying the risk indicator® disk three and four to men screened at initial and repeat screening within ERSPC Rotterdam [65].

Applying a nomogram that predicts biopsy outcome based on results of PSA, DRE, TRUS, prostate volume

(disk three in the risk indicator®) and having had a previous negative biopsy and choosing a probability cut-off of 15% or higher as trigger for prostate biopsy resulted 31% less biopsies in men initially screened and 46% less biopsies in men previously screened. The prostate cancer diagnoses that would have been missed when applying this biopsy indication consisted for res. 70% (initial screening) and 90% (repeat screening) of potentially indolent cases (calculated with disk four of the risk indicator®).

Conclusions

Whether or not the early detection of prostate cancer will save lives remains unknown at this moment. Implementing national population based screening programs will largely depend on the outcome of these trials. However it is very unlikely that screening for prostate cancer will be discontinued at this point in time and guidelines on how to screen for prostate cancer in a well-considered manner are an important need.

A nomogram that predicts the characteristics and course of the prostate cancer without invasive testing will very likely put an end on the most debated topic within the urological world, if it will ever become available. Using a nomogram should always be done with a critical mind since predictions on the presence or characteristics of the prostate cancer in an individual are based on study cohorts, with each having their own specific characteristics.

Therefore it is of up most importance to realize whether the nomogram that is used when counseling a patient is externally validated and applicable to his situation [66–68].

The ongoing randomized screening trials, the discovery of new biomarkers and the prospective treatment trials will without doubt provide the information needed to develop the ultimate nomogram for prostate cancer screening.

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