Defining and predicting indolent and low risk prostate cancer

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Abstract

The early detection of asymptomatic prostate cancer has led to the increased incidence of tumours that are unlikely to become symptomatic during life, so called indolent cancers. The prediction of low risk and indolent prostate cancer is needed to avoid overtreatment by unnecessary invasive therapies, and select men for active surveillance. Some of the currently available nomograms predicting these low risk tumours have been validated in independent populations. However, assessment to the compliance with their treatment advises based on the calculation of probability are scarce. The ultimate value of nomograms for the urologic practice can only be assessed by analysing their practical implementation.

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1. Introduction

The incidence of prostate cancer is increasing worldwide [1], likely due to an enhanced awareness of prostate cancer.

As the first evidence of a reduction of prostate specific mortality by screening of asymptomatic men between 55 and 70 years old was provided by the population based European Randomized study of Screening for Prostate Cancer (ERSPC) [2], and as in many parts of the world the overall life expectancy increases, individual men consider prostate cancer (PCa) screening for their personal benefit. App. 50% of PCa diagnosed in population based studies show the pathological features of the incidental cancers found at autopsy [3].
This implies that a subset of men diagnosed with prostate cancer do not require any active, invasive treatment during life. In the ERSPC, over 600 men with these clinically and pathologically defined low risk PCa features were observed without primary treatment over a period of ten years [4]. Overall survival was 70%, while none died of PCa.

The diagnosis of these small, well differentiated low risk tumours (i.e. over diagnosis), is the major drawback of screening for prostate cancer and the major barrier to implement population based PCa screening programs. Up to now there still is no parameter that can indicate the risk on an potential low risk cancer adequately before taking a prostate biopsy. For the same lack of strong prognostic markers also over treatment is difficult to avoid.

Various nomograms on the probability of low risk or indolent PCa have been constructed [5], in order to distinguish these cancers from those that are considered relevant at the time of diagnosis [6].

Since tumour monitoring with potentially delayed active invasive therapy (this is: active surveillance (AS)) has been included in the guidelines of PCa treatment, the selection of men suitable for an AS strategy based on accurate risk assessment has become pivotal. Guideline advice might vary substantially, likely related to the literature information they are based upon, and the cultural background of the health system, especially regarding the attitude for lawsuit procedures. While the American Urologic Association (www.auanet.org/guidelines) and the American Cancer Society (www.cancer.org) produced guidelines that define their low risk categories by PSA and Gleason score, the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology 2010 created an extra low risk category in addition to the low risk category adding other histological features, suggesting an extra safety level for the low risk categories by PSA and Gleason score only, the over treatment is difficult to avoid.

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Since tumour monitoring with potentially delayed active invasive therapy intervention might derive. The clinician then is most focused on the clinical distinction of indolent cancers from tumours that are relevant and need immediate treatment. For this, clinicians still use the set of parameters that have been developed based on the histologic studies of Epstein. Indolence therefore generally is still being defined by histologic features obtained in a diagnostic set of prostatic biopsies and can be described as clinically insignificant. In the near future genetic profiling of tumours may classify tumours in groups according to prognosis [9], and this genetic analysis of minute tissue volumes from needle biopsies is currently being validated [10].

2.2. Focal, insignificant, minimal or indolent?

2.2.1. Focal

Fig. 1 is an attempt to combine the various terms and aspects regarding low risk tumours for a clear understanding of their coherence. The term focal cancer has previously been used to indicate a single spot of low volume of cancer in biopsies or surgical specimens (less than 0.5 ml) observed by the pathologist on histology. Men with these cancers and a low Gleason score frequently belong to the group of patients that have a long and protracted course of their malignancy in the absence of symptoms (indicated by clinically insignificant cancers). Some of these very small cancers nevertheless have been reported as potentially aggressive [11] due to a poor tumour differentiation, which shows that not all low-volume disease is expected to have a benign course. Such tumours correspond with area 5 in Fig. 1. Tumour size as a...
criteria for minimal or insignificant disease has been defined differently over time, often as less than 0.2 [12], 0.5 [13], or 1.0 ml, but always in combination with a Gleason sum 6 or less. Remarkably, these criteria have been validated only recently in population based series [14]. In the ERSPC data set, the volume of the index tumours in radical prostatectomy specimens was correlated with life time risk on symptoms, showing that for tumour stage less than T2b, and Gleason sum less than 7 the threshold volume for significance was 1.3 ml for a single or index lesion, and 2.5 ml of total tumour volume. In fact, nomograms predicting smaller tumours could be adjusted for this validated threshold.

2.2.2. Insignificant

The cancer growth determines the clinical fate of the tumour. Tumour growth is by nature continuous, but in case of indolent tumours expected to be slow. Doubling times of tumour growth of over 10 years have been measured directly or indirectly with PSA measurements [15]. It is theoretically possible that for example multifocal or larger sized tumours (more than 1.3 ml) exist with a slow biologic growth, in which case these tumours remain asymptomatic. We know little about such cancers, as data on the follow-up of such tumours visualized by ultrasonography [16] or MRI [17] is only just emerging. And most larger tumours are likely subject to therapeutic interventions, as they are not expected to remain asymptomatic. These tumours correspond with area 6 in Fig. 1.

2.2.3. Minimal

The clinical diagnosis of indolence, i.e. minimal disease (Fig. 1 lowest circle) uses criteria derived from autopsy information and radical prostatectomy specimens described by Epstein already in 1993 [18]. These were enriched towards clinical Epstein criteria by a combination with parameters like PSA and prostatic volume, and biopsy pathology parameters [19]. They are: PSA < 10 ng/ml, PSADensity < 0.15 ng/ml/ml, less than 3 positive cancer cores, no Gleason 4 or higher, Gleason sum 6 or less, and less than 50% cancer in a biopsy core. Histologic and clinical criteria formed the base for the construction of nomograms that have been improved ever since with the increasing clinical experience. It is likely that sooner or later genomic or proteomic markers from ongoing research will be added.

Identical criteria have been used to select men for active surveillance programs. From these programs it is well known that 30–40% of men show tumour progression or reclassification during the first four years of follow-up [20]. These are the men that are unlikely to have an overlap with the slow growing tumours, therefore leaving the areas 1 till 4 in Fig. 1 as the most likely areas to incorporate real indolent tumours, and generally move from inside to outside the circles of Fig. 1. There must, however, be some tumours that are reclassified due to their biopsy results and might have remained biologically insignificant (area 6), just as there might be tumours that clinically remain similar to minimal disease, but are biologically active (area 7) and ultimately even metastasize. Schemes, like Fig. 1, and generally accepted definitions might support professional discussions, and the validation of data sets, and they might help to illustrate the classification changes over time.

3. Current nomograms predicting indolent cancer are integrated in risk assessment strategies

The development of nomograms to predict the outcome of disease treatments has been stimulated by the growth of clinical databases overtime. Nomograms are of interest to inform patients, and support them making treatment choices. Nomograms also classify patients in risk groups that are used to select patients for clinical trials.

Current nomograms for predicting indolent cancer (at the time cancer has been diagnosed) are based on the histological evaluation of step-sectioned radical prostatectomy specimens from various populations, being clinical referral patients or men from the general population in a screening setting. This histopathological surrogate endpoint has to be validated over time in active surveillance programs. The difference in study populations between the various nomograms has been acknowledged as the predominant factor responsible for the differences between the nomograms constructed so far [21]. This also raises questions about the generalisibility of nomograms.

The currently available nomograms have been discussed extensively in a previous paper [5]. The nomogram of Kattan for the prediction of indolent cancer was initially created in 2003 [22] and updated in 2007 on the website of Memorial Sloan Kettering Cancer Centre, as it was recognized that the study population gradually changed in composition during the last five years (www.mskcc.org).

The Steyerberg nomogram was constructed from 247 stage T1c or T2a patients from the ERSPC with a biopsy Gleason sum of 6 maximum, number of positive cores less or equal to 50%, total cancer in biopsy cores less or equal to 20 mm and benign tissue in all cores at least 40 mm. All were treated with radical prostatectomy [21]. Overall 121 (49%) of 247 patients had indolent cancer in the radical prostatectomy specimen according to the Epstein criteria. Predictions in men with screen-detected cancers covered a wide range with 60 of 278 (22%) having probabilities below 30%, and 84 of 278 (30%) with a probability of more than 60% having an indolent cancer. This nomogram could identify about 30% in a screening population having indolent disease. The concept of indolent disease was validated in the ERSPC population, showing 100% cancer specific survival over 8 years follow-up [4,23]. Thus, in the screening setting it was possible to predict a high probability of indolent cancer in a third of the men fulfilling the strict selection criteria for this evaluation.

These two nomograms of Kattan and Steyerberg were compared and validated in a separate screening cohorts, and showed an excellent discrimination level expressed as AUC of 77% [24].
Recently the Steyerberg nomogram was updated with a correction factor for the use of 12 or 18 cores prostate biopsy schemes instead of the 6 core biopsy scheme which was applied in the development cohort [25].

The Nakanishi nomogram in 2007 restricted the construction of a nomogram to men with only one positive core on twelve prostatic biopsies [26]. All men underwent radical prostatectomy, and indolent disease, defined as pathologic organ-confined with a tumour volume <0.5 ml without Gleason grade 4 or 5 cancer, was found in 52% of cases. Parameters used were age, PSA, prostate volume, and tumour length in a biopsy core.

A different approach was chosen for the construction of the Kattan/Cuzick nomogram, using 10-year disease-specific survival (and not surgical tumour volume) as a base. In a large population based cohort of 1911 men who received no initial active prostate cancer therapy in 6 cancer registries within England and numerous hospitals in the USA, a nomogram using grade, PSA and stage was constructed for the prediction if not treated immediately [23]. The nomogram was validated in a different cohort of men, showing a concordance index of 0.73, and good calibration.

We have to realize that the construction of nomograms discussed and their individual probability outcome calculated is likely dependent on the upfront selection of men that undergo prostate biopsies. As Vickers and Roobol showed for men that ask themselves whether they have to be screened, when using risk stratification based on DRE, PSA and prostate volume to select men for biopsies, a large subset of men with potentially low risk tumours is advised not to follow a diagnostic procedure compared to the situation in which only a PSA cut-off value is used as a biopsy selection criteria [27]. These men are informed on their very low risk of having a detectable cancer. Risk based strategies for biopsy, as provided by the ERSPC PCa risk calculator (www.uroweb.org) or the PTCP risk calculator (www.ptcp.org) will have a direct effect on the performance of calculators for indolence in men subsequently diagnosed with cancer. It is likely best to use the set of ERSPC calculators as a whole, in the geographical area in which they have been validated (Northern Europe), while using the PTCP calculator, which also includes information on black Americans, in the USA. Nevertheless, for white Americans, the ERSPC risk calculator performed better in white Americans compared to the PTCP calculator, as the ERSPC instrument includes prostate volume in its calculation of probability [28]. Direct head to head comparisons of the two risk calculators have been published recently and show that overall the ERSPC risk calculator has better discriminatory capability [29–31].

4. The use of nomograms in the setting of the host

The use of nomograms has been evaluated by Cooperberg, who reported on the existence of over one hundred of predicting tools in the field of Urology [32]. On their implementation in the daily practice it is quoted ‘…Clearly, no risk instrument should be used in isolation to direct patients towards or away from treatment alternatives…’ This is a serious warning to incorporate various host related factors to take clinical decisions. Factors not measured by current models are for example: baseline quality of life, comorbidity, life expectancy, and treatment preference.

The importance of comorbidity for PCa treatment decisions, or even for screening, was recently highlighted by Albertsen et al. [33], illustrating the influence of the Charlson et al. score [34] on overall and tumour specific survival. For example, for men aged 66–75 diagnosed with a PCa staged T1c with a Gleason sum of 7 or less, a Charlson score of 2 or more increases overall mortality by approximately 3-fold over a period of twenty years (10-year mortality rate per 100 from 28.8 to 83.1) compared to a Charlson score of 0. This while the tumour specific mortality rate remained stable with 4.8–5.3%. Using this comorbidity information for individual predictions is preferable to overall statistics of life expectancy on a population level that provide a robust but only very general impression.

5. The implementation phase of nomograms

In order to implement nomograms into the daily urological routine, a series of validations needs to be followed after the initial construction phase. Traditionally, a nomogram would be tested on an independent but relevant population set, such as has been performed for the predictive ERSPC risk calculator [35]. Next, an evaluation of the implementation should take place to analyze the impact of the instrument as a decision tool on the actions taken by patients and physicians. This phase is rarely completed, however, would provide important information on current questions on the hesitance of physicians and patients on the use of risk assessment tools.

The compliance with biopsy recommendations provided by the ERSPC prostate cancer risk calculator was evaluated by van Vugt et al. (accepted for publication BJU 2011). In a setting in which 291 men with a request for PCa screening agreed to submit themselves to the use of this risk assessment instrument, 84% were compliant with the advise to biopsy or to refrain from it. Remarkably the most important reason for non-compliance of the 31 of 119 men that were advised not to be biopsied, was the reluctance of the physicians due to the PSA level as a single parameter. It showed that the traditional biopsy threshold of PSA over 3 ng/ml overruled the advise given by the nomogram.

Analysis of the compliance to a risk calculator on the probability of low risk, or indolent, PCa was also performed by van Vugt [BJU under review 2011]. In five Dutch hospitals a prospective analysis was done for nearly 300 men initially selected with: clinical stage T1c, T2a-c, PSA <20 ng/ml, <50% positive sextant biopsy cores, ≤20 mm cancer, ≥40 mm benign tissue, and Gleason ≤3+3. An advise for active surveillance was given when the probability of the
ERSPC risk calculator exceeded 70%. Of all men included 55% (50/213) were advised AS, and 84% of men was compliant with this advise. Remarkably of those men advised to follow active treatment, 30% chose active surveillance after obtaining their probability score, in contrast to the active treatment recommendation. As a result, this recommendation is used in the authors’ institute (Erasmus MC, Rotterdam) to illustrate to the patient eligible for inclusion in the PRIAS project his probability on an indolent cancer. As the nomogram has been developed on data from the age group 55–74 years old, patients aged 75 or older are not offered active surveillance (but watchful waiting if conservative treatment is indicated based on life expectancy). Patients younger than 55 diagnosed with minimal low risk disease often consider a conservative approach for some years in order to delay potential side effects like erectile dysfunction of invasive treatment. In the absence of a proper risk calculator for this age group, an active surveillance strategy can be offered with adequate data registration.

According to Kattan [in this journal], traditional statistical techniques do not evaluate not clinical consequences, and therefore are not cable of informing the clinical practice well. Decision curve analysis is used to calculate clinical net benefit [36]. This decision curve analysis informs about the clinical value of a model where traditional accuracy metrics do not working with sensitivity and specificity and AUC curves [www.decisioncurveanalysis.org]. This method would not need further data on patient preferences, or costs of effectiveness.

6. Improving nomograms

Current nomograms on the presence of low risk or indolent disease still lack the long term clinical follow-up on surveillance. With time, the current AS programs [20,37–40] will provide this information, improving the accuracy of predictions. New prognostic parameters related to the low volume low grade tumours found by radical prostatectomy will be validated and incorporated in the nomograms. Candidate markers at presence are the kallikreins [41] proPSA [42], PCA3 [43], or histologic markers [44]. Next to these, imaging is expected to play a larger role in the initial assessment of risk, as it is to be in the monitoring of men on active surveillance. In a series of 114 men on active surveillance, positive MRI lesions had a higher risk of upgrading compared to men with normal MRI’s [45]. Also parameters in diffusion weighted MRI changed more in progressors over time, than in non-progressors [46].

The accuracy of nomograms can not only be improved based on the addition of new parameters, the sample size and duration of follow-up, but also by the model used, and the more accurate measurement of the individual parameters, that is: cleaner data [47]. Having cleaner data starts at the time of inclusion with an adequate number of initial biopsies in relation to the prostate volume. It is often seen that an inadequate number is corrected by a second biopsy only after 6–12 month, which is then regarded as a ‘follow-up’ restaging biopsy instead of an ‘inclusion’ biopsy. The evaluation of an early repeat biopsy is therefore compromised, and the current value of a repeat biopsy after 3–6 months compared to a restaging biopsy after 12 months is unknown.

7. Conclusions

Nomograms provide us with tools to inform patients and physicians more objectively with information on present conditions and future events. They allow us to take a step back and review the experience of many observers, independent on the recent individual impressions on a disease. When complex decisions have to be made using various parameters, nomograms can support balancing the weight of each individual parameter. However, the definition of thresholds for treatment advises is still heavily influenced by what we find ‘acceptable’ as a risk. In the urologic practice we consciously or unconsciously make such decisions permanently. For example by accepting the predictive performance of a serum marker or an image report, knowing that their accuracy is often not higher than 70–80%.

In low risk disease existing nomograms can provide a probability score for the presence of an indolent disease. Some nomograms appear to be sufficiently robust to be used in larger geographical areas outside the population where they have been raised. Continuous awareness on the conditions in which they are applied (that is the preselection of the population by other interventions), and the clinical outcome over time (the maturing of data) is needed to improve the nomograms, and to obtain the best predictive results. There is an increasing confidence in the use and compliance to treatment advises by patients as well as physicians.

Conflict of interest

None.

Reviewers

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References


Biography

Chris H. Bangma (born 4th January, 1959) was nominated Professor and Chairman of the Department of Urology at Erasmus University Medical Centre in Rotterdam, The Netherlands, in 2002. He wrote his Ph.D. thesis on ‘Prostate Specific Antigen and ultrasonography in detection and follow-up of prostate cancer’ in 1995, and completed his professional urologic training at the same institute in 1997. He was granted a research fellowship on gene therapy for prostate cancer by the Dutch Cancer Society, and spent a two-year period at Baylor College of Medicine, Houston, USA, with Prof Timothy Thompson and Peter Scardino, and afterwards at the oncology lab of Prof. Bob Pinedo at the Free University in Amsterdam. Chris Bangma participated in the European Fifth Framework Program from 2000 onwards on the preclinical development of gene therapeutic vectors, followed by coordinating the clinical application in the GIANT consortium within the European Sixth Framework Program. He has participated to the European Randomized study on Screening of Prostate Cancer ERSPC from its start in 1992 as a board member, and has coordinated the P-Mark consortium since 2004 till 2008 under the umbrella of the Sixth Framework Program for the search and validation of prognostic serum markers for prostate cancer. Furthermore, he is PI of the PRIAS (Prostate Cancer International Study of Active Surveillance), PROCABIO (Prostate Cancer Biomarker research in clinical setting of Active Surveillance, a European initiative to develop tailored treatment of prostate cancer by biomarkers), ZonMw Translational Genetherapeutisch Onderzoek (Oncolytic adenovirus therapy as a neoadjuvant treatment for prostate cancer), PRO-NEST (Prostate Research Organizations-Network of Early Stage Training, 7th Framework EC, Peoples Program), and PCMM (Prostate Cancer Molecular Medicine, the Dutch integrated academia–industry program) programs/studies. Chris has contributed to over 150 peer reviewed papers predominantly in the field of prostate and bladder carcinoma. Currently he is president of the Dutch Urologic Society.