Updating the prostate cancer risk indicator for contemporary biopsy schemes

Meelan Bul, MD,[1] Nicolas B. Delongchamps, MD,[2] Ewout W. Steyerberg, PhD,[3] Gustavo de la Roza, MD,[4] Pim J. van Leeuwen, MD,[1] Xiaoye Zhu, MD,[1] Heidi A. van Vugt,[1] Gabriel P. Haas, MD,[5] Fritz H. Schröder, MD,[1] Monique J. Roobol, PhD[1]

[1]Department of Urology, Erasmus MC, University Medical Center, Rotterdam, The Netherlands
[2]Department of Urology, Cochin Hospital, Paris Descartes University, France
[3]Department of Public Health, Erasmus MC, University Medical Center, Rotterdam, The Netherlands
[4]Department of Pathology, SUNY Upstate Medical University, Syracuse, New York, USA
[5]Astellas Pharma Global Development Inc, Deerfield, Illinois, USA

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Introduction and objective: *The prostate cancer risk indicator is a validated tool for predicting the chance of a screen detected prostate cancer to be classified as indolent, partially based on lateralized sextant biopsies. Our objective is to extract correction factors for adjustment of the model, addressing contemporary extended biopsy schemes.*

Materials and methods: *Post-mortem 18-core biopsy results of men who died of unrelated causes, but were diagnosed with prostate cancer post-mortem were used to provide details on prostate biopsies and whole mount specimens. For each of the 18-core biopsies showing cancer, Gleason score, number of positive cores, location in the gland and percentage of cancer involvement were determined and correlated to final pathology. Total length of cancer tissue in a 6-core scheme was related to the length in 12 and 18-core schemes to compute correction factors. Furthermore, upgrading on extended biopsies and final pathology was evaluated.*

Results: *Data from 33 autopsied men were included. The 18 and 12-core biopsies showed 192.72 mm and 143.76 mm of prostate cancer, compared to 70.80 mm with lateralized sextant biopsy, resulting in correction factors of 2.72 and 2.03 for 18 and 12-core schemes respectively. Upgrading in Gleason score on extended biopsy regimens compared to lateralized sextant biopsy occurred in 33% (11/33) of the cases.*

Conclusion: *Based on autopsy data, the present correction factors provide a support in the adjustment of the prostate cancer risk indicator towards more extended contemporary biopsy schemes, eventually leading to a more accurate prediction of the probability of indolent cancers and assisting patients and clinicians to make appropriate choices in daily practice.*

Key Words: early detection, needle biopsy, nomograms, prostatic neoplasms

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Address correspondence to Dr. Meelan Bul, Erasmus MC, University Medical Center Rotterdam, Department of Urology, Room NH-224, P.O. Box 2040, 3000 CA Rotterdam, The Netherlands

Introduction

Screening with serum prostate-specific antigen (PSA) was shown to reduce the rate of death from prostate cancer by 20% in the European Randomized Study of Screening for Prostate Cancer (ERSPC).[1] This rate could even be improved when it was adjusted for non compliance and contamination.[2] In contrary, the first results of the Prostate, Lung, Colorectal and Ovarian (PLCO) screening study did not show a decrease in mortality,[3] but selective use of PSA screening for men in good health was found to reduce the risk of disease-specific mortality in this trial.[4] However, concerns have been raised on over diagnosis[1,5,6] and over treatment of tumors which may not be harmful. Men with low

grade prostate cancer often die of other causes before these tumors become harmful[7] and radical treatment is associated with serious side effects.[8,9] The percentage of prostate cancer detected during screening in men who would not otherwise have clinical symptoms during their lifetime, has been estimated to be as high as 50%.[10]

Prognostic models have been designed to predict indolent prostate cancer.[11] Steyerberg et al[12] updated and validated a nomogram, that is now applied in level 6 of the prostate cancer risk indicator, www.prostatecancer-riskcalculator.com, Figure 1. This nomogram predicts the probability of clinically indolent prostate cancer (i.e. prostate cancer not causing any comorbidity or mortality based on favorable tumor characteristics, irrespective of patient related factors) detected by screening and can support patients and clinicians when considering different treatment options. These predictions are based on the length (in mm) of prostate cancer sampled in sextant biopsies (from the Rotterdam arm of the ERSPC), which limits its applicability for contemporary practice where often extended biopsy regimens are used. In order to allow predictions based on 12-18 core biopsy regimens we analyzed the data of recently published autopsy studies,[13,14] after establishing cooperation which allowed access to the original data, and extracted adjustment factors for specific biopsy schemes.

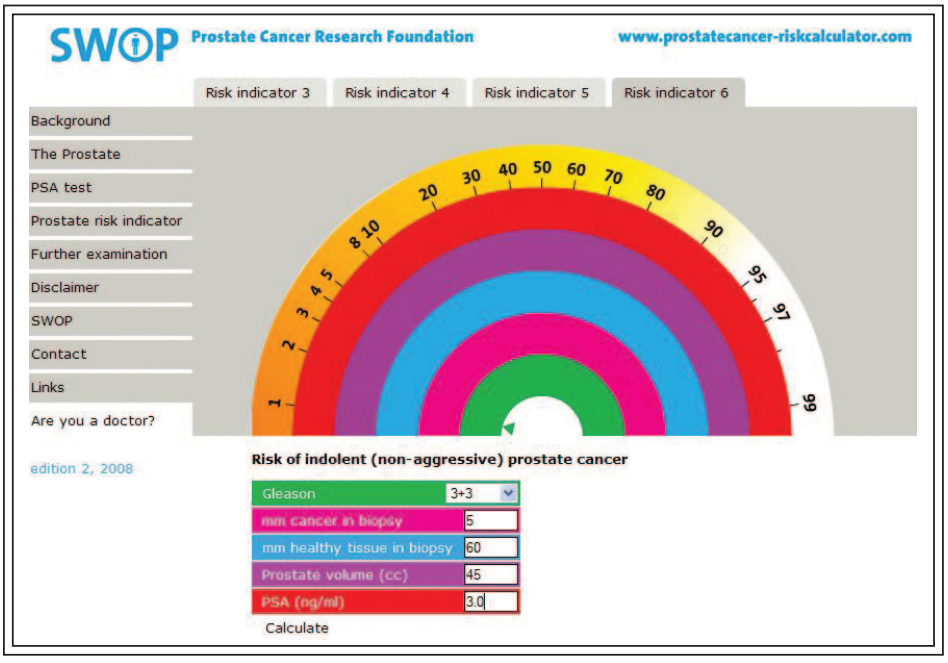

Figure 1. Prostate cancer risk indicator, level 6.
The boxes under the graph can be completed with Gleason score, PSA, prostate volume and length of cancerous and healthy tissue in the biopsy in order to predict the probability of indolent prostate cancer.[12]

Materials and methods

We analyzed the percentage of tumor involvement per biopsy core from two autopsy studies investigating the true sensitivity and specificity of 6, 12 and 18-core biopsies,[13,14] to allow predictions based on contemporary 12 to 18 core biopsy regimens by deriving adjustment factors for specific biopsy schemes. In these studies 18-core needle biopsies were performed on prostates (ex vivo) obtained at autopsies of men who died of unrelated causes (n = 212) and of whom only age, race and cause of death were recorded. All biopsies were performed in a manner that mimicked clinical biopsy under the direction of a urologist. Biopsies were taken with a standard 18F spring-loaded biopsy gun (Bard MaxCore, C.R. Bard, Covington, GA, USA). The biopsy gun needle was inserted through the posterior surface of the hand-held gland and bilateral samples were taken from the apex, mid gland and base. Six-core biopsies were taken from the mid peripheral zone, the lateral peripheral zone and the central zone. For each biopsy showing cancer, Gleason score, the number of tissue cores containing cancer, the percentage of cancer involvement in each core and the location of the tumor in the gland were determined. The Gleason score on biopsy was correlated to the Gleason score on final pathology of the prostates. Each tumor focus was graded according to the modified Gleason grading system.[15] The lateralized sextant biopsy regimen of the ERSPC (red circles, Figure 2) was compared to the 12 (red and blue circles) and 18-core (all circles) regimens of the autopsy study. The length (in mm) of cancer tissue in each biopsy core was recorded. The total length of cancer tissue found with the sextant biopsy approach was related to the 12 and 18-core biopsy scheme. Gleason score and possible upgrading per biopsy regimen were evaluated. Furthermore, the nomogram probability of indolent disease was evaluated in the case of a 6, 12 or 18-core regimen, with and without making use of the correction factors respectively. For the purpose of this study, all prostate cancer cases were

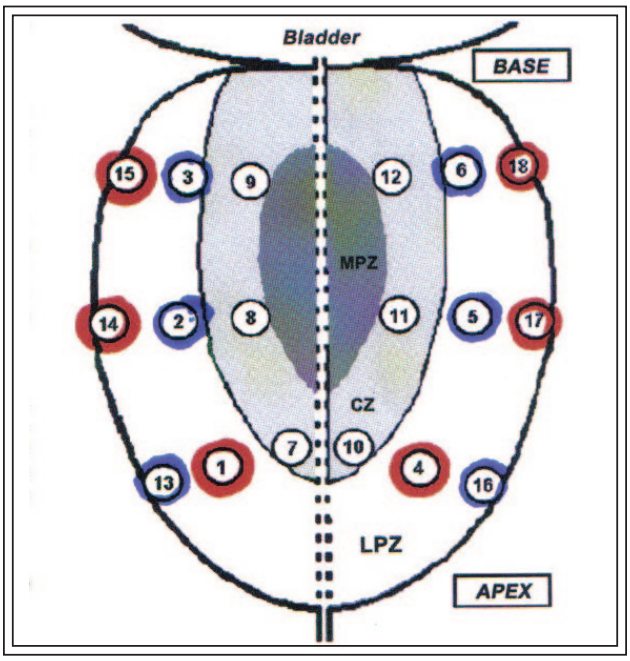

Figure 2. Biopsy scheme autopsy study.
Biopsy scheme for the 18-core needle biopsies with the red circles representing the sextant biopsy regimen of the ERSPC and the red and blue circles together representing the 12-core regimen.[13]
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considered to be indolent, as none of the subjects were diagnosed with prostate cancer during life nor died of the disease. A nomogram predicted chance ≥ 70% for indolent disease was used as a cut off value, because of a good sensitivity-specificity trade-off with detection of 94% of clinically important prostate cancer.[12]

Results

Prostate cancer was found on whole mount sections in 59 of 212 men (28%). Prostate biopsies detected cancer in 33/59 patients (56%). In all of these patients, detailed information on percentage tumor involvement per single biopsy core was known. Median age was 72 years (range 49-92 years). Median prostate volume was 50 cc (range 23 cc-95 cc). The mean length of the biopsy cores in the 33 autopsy cases was 12 mm per core, which is similar to the mean length in the ERSPC.[1] The 18-core and 12-core biopsy regimen sampled a total of 192.72 mm and 143.76 mm of prostate cancer respectively. The lateralized 6-core regimen (biopsy technique of the ERSPC) sampled 70.80 mm prostate cancer tissue. These data translate into correction factors of 2.72 (192.72/70.80) if a biopsy scheme of 18 cores is used and of 2.03 (143.76/ 70.80) with a 12-core biopsy scheme. The total length in mm of benign tissue can be multiplied by 2 or 3 in case of a 12 or 18-core biopsy scheme respectively.

Upgrading in Gleason score on extended biopsy regimens compared to lateralized sextant biopsy is depicted in Table 1. There was under grading on sextant biopsy in 33% (11/33) of cases. The biopsy results are compared to final pathology in Table 2. In one case, prostate cancer was detected with biopsy, but could not be located in the whole mount specimen. The concordance rate was 70% (23/33) in total and 52% (17/33) for the prostate cancer diagnosed with a sextant regimen. The under grading rates were 18% (6/33) and 39% (13/33) respectively.

Discussion

Prostate cancer is the most common (non-cutaneous) cancer in US males and the second most important cause in cancer related deaths with estimated numbers of 192,280 and 27,360 in 2009[16] and numbers of 382,000 and 89,000 in Europe in 2008 respectively.[17] Due to PSA-based screening, the time of diagnosis of prostate cancer has advanced considerably and a substantial over diagnosis is observed in up to 50% of the cases, meaning that half of the men screened would not have ever been diagnosed with prostate cancer in their lifespan in the absence of screening.[10] With these prostate cancer being detected, improvement of outcome predictions by proper staging is a major issue. In order to predict indolent prostate cancer and to subsequently reduce unnecessary radical treatment, nomograms that predict the chance of potentially

TABLE 1. **Gleason grading on lateralized sextant biopsy and extended biopsy regimens. Upgrading on extended biopsy regimens is shown in bold (12 or 18-core).**

	Gleason score on extended biopsy regimens			
	3 + 3	**3 + 4**	**4 + 4**	**4 + 5**
Gleason score on lateralized sextant biopsy				
3 + 3	18			
3 + 4		3	**1 (12)**	**1 (12)**
4 + 4			1	
No prostate cancer	**5 (12)** **1 (18)**	**2 (12)**	**1 (12)**	

TABLE 2. **Gleason grading on biopsy and final pathology. Upgrading on final pathology is shown in bold.**

	Gleason score on extended biopsy				Gleason score on lateralized sextant biopsy				
Gleason score on final pathology	**6**	**7**	**8**	**9**	**6**	**7**	**8**	**9**	**No prostate cancer**
6	18		1		14	1			**4**
7	**5**	5	1		**3**	3	1		**4**
8				1		**1**			
9			**1**						**1**
No prostate cancer	1				1				

indolent disease can be used, for example level 6 of the prostate risk indicator. This nomogram[12] was validated and updated with 247 patients from the ERSPC who were treated with radical prostatectomy and contains the following predictive characteristics: serum PSA, ultrasound prostate volume, clinical stage, biopsy Gleason score and total length of cancerous and noncancerous tissue in biopsy cores. Indolent disease was defined as a combination of a total tumor volume less than 0.5 mL, no extracapsular extension and no Gleason score 4 or 5. Selection criteria for the 247 patients were: age group 55-74 years, clinical stage T1C/T2a, PSA ≤ 20 ng/mL, primary or secondary GS ≤ 3, 50% or less positive cores, 20 mm or less total cancer in biopsy cores and at least 40 mm benign tissue in all cores. When applying both the Kattan nomogram[11] and the Steyerberg nomogram[12] to a recent, clinical population, the resulting AUC of the ROC curve for predicting indolent disease were 0.779 and 0.777 respectively, indicating good and comparable discrimination for both models.[18]

In this manuscript we proposed a correction factor for contemporary 12 and 18-core biopsy regimens based on autopsy data, to support future conversion of the risk indicator to predict the probability of indolent cancers on a more accurate prostate sampling. Correction factors of 2 and 3 for benign tissue and 2.03 and 2.72 for malignant tissue, respectively for 12 and 18-core biopsy regimens were calculated. These values are indicative, but still have to be validated before they can be used to predict a more precise outcome for extended biopsy regimens than the sextant biopsy on which the risk indicator was originally based. These results accentuate that it is inaccurate to use default correction factors of 2 and 3 for 12 and 18 cores respectively. The calculated correction factors implicate that the length of prostate cancer tissue would be divided by 2.03 and 2.72 with biopsy regimens of 12 and 18-cores, respectively. Although not yet validated, these findings give direction to the improvement of the clinical applicability of the risk indicator, because changes in clinical practice have led to the use of larger numbers of biopsies often compatible with the 12 and 18 cores applied in our autopsy series.

Extended biopsy regimens result in significantly higher detection rates as compared to earlier sextant protocols.[19] The incidence of prostate cancer is not equally distributed throughout the prostate, with the peripheral zone being affected more often.[20,21] In this study lateralized sextant biopsy detected 24/33 (73%) patients with prostate cancer. The nine prostate cancers that were not diagnosed based on lateralized sextant biopsy, were detected on 12-core biopsy in four cases, on 18-core biopsy in one case and on a combination of both in four cases. This implies that 97% (32/33) of PC cases were detected on 12-core biopsy. Scattoni et al state that the 12-core sample seems reasonable to consider as an initial prostatic biopsy, with saturation techniques not demonstrating to improve cancer detection, but with significantly superior results compared to the standard sextant biopsy.[19] Schröder et al[22] found lateralized sextant biopsy to be an adequate and safe regimen if *repeated* screening is applied. Furthermore, they stated that, based on a review of literature, lateralized sextant biopsy would miss 19% of cancers detectable with more extensive schemes. This is a smaller amount than the 27% we found in this study. In the screening study of the Rotterdam section of the ERSPC, missed or delayed diagnosis did not appear to result in increased progression or cancer specific mortality.[22]

Three of the patients with cancer on sextant biopsy showed an upgrading of Gleason score with the extended biopsy regimens, resulting in an underestimation of Gleason score by sextant biopsy in 8.3% of the cases. Noteworthy is all three of these patients would not have fitted the active surveillance protocol we use at our center[23] following any of the biopsy regimens and would thus have had the advice for radical treatment. Prediction of the final Gleason score in this cohort by biopsy results for the sextant regimen and the 18-core regimen showed 52%-70% concordance rates respectively. In literature[19] similar

concordance rates have been reported of 28%-48% and 63%-72% respectively.

Besides Gleason score, we did not further compare the predicted outcome of the risk indicator to the final outcome on pathology, because all the cancers were by definition clinically insignificant as none of them were diagnosed during life. Also, the age and PSA distribution of this cohort deferred of that of the cohort on which the nomogram was validated and no information on clinical stage was available for the autopsy specimens.

Limitations of this study include the small number of patients and the lack of validation of the results. Additionally, the calculated correction factors are restricted to 12 and 18-core biopsy schemes with a mean length of 12 mm per core. Not all pathologists may report on the exact length of cores and cancerous tissue, which potentially makes it a more difficult value to acquire. This study population does not exactly match the population used to create level 6 of the risk indicator concerning the selection criteria mentioned above, thus caution should be used when interpreting these results. Previous negative biopsies during lifetime would represent a selection bias and could not be excluded in the autopsy series.

Conclusion

The outcome of this study contributes to the improvement of the prostate cancer risk indicator, providing a support in the adjustment towards more extended biopsy schemes, eventually leading to a more accurate prediction of the probability of indolent cancers, which will enable its use with the extended biopsy regimens in contemporary practice. As a result, patients and clinicians can be assisted in making more appropriate treatment decisions. Further validation of these results is needed to justify the use of these correction factors in contemporary practice. □

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