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Optimising repeat prostate biopsy decisions and procedures

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To review strategies to optimise repeat biopsy procedures and to better predict the biopsy outcome. As it is often uncertain whether a repeat biopsy should be performed in men with ≥1 previous negative prostate biopsies but persistent suspicion of prostate cancer. The repeat biopsy may also be negative and a biopsy may be associated with anxiety, discomfort and occasionally (severe) complications. A search in PubMed was performed to find English language original and review articles related to repeat prostate biopsies. Strategies to optimise repeat biopsy procedures include applying the appropriate indications and adjusting the location and number of biopsy cores. The PROGENSA™ Prostate CAncer gene 3 (PCA3) Assay is a highly prostate cancer-specific test. A higher PCA3 Score corresponds with an increased probability of a positive repeat biopsy and including the PCA3 Score in multivariate models significantly increased their predictive accuracy for predicting repeat biopsy outcome. The PCA3 Score seems also to be predictive of future biopsy outcome. In clinical practice it is often uncertain whether a prostate biopsy should be repeated or not. Optimising repeat biopsy procedures and the use of diagnostic markers, such as PCA3, can increase the probability of a positive repeat biopsy and reduce the number of unnecessary and uncomfortable biopsies

What's known on the subject? and What does the study add?

Due to the fear of missing clinically significant cancer, it is often uncertain whether a repeat biopsy should be performed in men with ≥1 prior negative prostate biopsies but persistent suspicion of prostate cancer. However, the repeat biopsy may again be negative and a biopsy may be associated with anxiety, discomfort and complications (resulting in hospitalisation in 4.1% of men).

This review discusses strategies to optimise repeat biopsy procedures in order to better predict the biopsy outcome. Optimising repeat biopsy procedures include adjusting the location and number of cores and the use of MRI to detect suspicious areas. The use of diagnostic markers, e.g. (Prostate CAncer) gene 3, which is predictive of biopsy outcome, can aid in guiding repeat biopsy decisions and reduce the number of unnecessary and uncomfortable biopsies.

KEYWORDS

Prostate CAncer gene 3, PCA3, prostate cancer, diagnosis, repeat prostate biopsy

INTRODUCTION

Men with ≥1 previous negative prostate biopsies, but persistent suspicion of prostate cancer based on, e.g. a persistent elevated/rising PSA level and/or a suspicious digital rectal examination (DRE) present a dilemma to the urologist. Should a repeat biopsy be performed or not, as there may be concern that the cancer was missed at the initial biopsy. In men with suspicion of harbouring prostate cancer and ≥1 previous negative biopsies, a repeat biopsy has shown to be positive in 10–35% of cases [1,2]. The adequacy of the initial biopsy (e.g. number of cores) needs to be considered, but even after an initial extended (21-core) biopsy, prostate cancer has been detected in 18%, 17% and 14% of second, third and fourth saturation biopsies [3]. The patient may also harbour a precancerous condition, e.g. having atypical small acinar proliferation (ASAP), that may progress. In a follow-up study of 164 men with an elevated PSA level and an initial negative biopsy, 11% developed prostate cancer within 7 years [4]. Because of the concern of a missed or progressing cancer, a repeat biopsy is a frequent decision taken by urologists confronted with this dilemma. However, as outlined above there is a considerable probability that this biopsy will also be negative. A (repeat) biopsy may also induce anxiety for the patient and his family because of fear for the procedure and still harbouring prostate cancer. In addition, 5–90% of patients report discomfort or pain after a TRUS-guided biopsy [5]. This may arise from puncture of the prostatic capsule and stroma, although some men also find the introduction and presence of the ultrasound (US) probe within the rectum uncomfortable [5]. Prostate biopsies may also be associated with complications of greatly varying incidence depending on the study methods used (Table 1). Although most complications can be considered minor, their rate is relatively high. More severe complications such as urinary retention occur in 0.2–10% of men and hospitalisation for severe haematuria, infection or even life-threatening septicaemia may be required in up to 4% [7]. The percentage of men hospitalised for infection after biopsy also seems to be increasing [7]. The reason for this is not known but may be due to an increase in the

TABLE 1 Complications of prostate biopsy (adapted from [6])

Complication	% of men
Haematuria	12.5–80
Haematospermia	5.1–89
Rectal bleeding	1.3–58.6
Urinary retention	0.2–10
Hospitalisation	0–4

number of cores taken and/or bacterial resistance. Fear of biopsy associated pain, discomfort and complications may increase anxiety and discourage men with a prior negative biopsy but with remaining suspicion of prostate cancer of having a repeat biopsy. About one in 10 men refuse a repeat biopsy or require sedation or analgesia because of fear of complications and/or discomfort [5]. Therefore, procedures to increase the probability that a repeat biopsy will be positive are sorely needed. In addition, strategies that may lead to a more informed decision whether a repeat biopsy is indeed necessary, thereby reducing the number of unnecessary biopsies, would be most welcome. This review discusses several strategies to optimise repeat biopsy procedures and biopsy decisions based on recent review articles and original papers.

MATERIALS AND METHODS

A search in PubMed was performed in January 2011 to find English language original and review articles related to repeat prostate biopsies and Prostate CAncer gene 3 (PCA3). This was performed by using Medical Subject Headings (MeSH) search terms 'Prostatic Neoplasms', 'Biopsy', 'prostate cancer antigen 3, human' and free-text terms 'prostate cancer', 'prostate biopsy', 'repeat biopsy', 'PCA3', 'prostate cancer gene 3' alone and in combination. References of review articles were also screened to find relevant articles.

PROCEDURES TO INCREASE THE PROBABILITY OF A POSITIVE REPEAT BIOPSY

Procedures that may increase the probability of a positive repeat biopsy include applying appropriate indications and optimising the biopsy procedure by adjusting the number and location of biopsy cores [1].

INDICATIONS FOR REPEAT BIOPSY

The European Association of Urology guidelines state that the indications for a repeat biopsy are a rising and/or persistent elevated PSA level, a suspicious DRE and/or ASAP [8]. The National Comprehensive Cancer Network (NCCN) clinical practice guidelines indicate that PSA velocity and adequacy of initial biopsy such as number of cores (recommended by NCCN to be minimally 12), location and prostate size must also be considered when deciding on repeat biopsy [9]. High-grade prostatic intraepithelial neoplasia as an isolated finding is no longer considered an indication for repeat biopsy but is only considered when it occurs multifocally [8]. Other prostate cancer risk factors, e.g. family history or African-American race, have not been evaluated as potential indications for repeat biopsy but often affect the urologist's decision [10]. Patient anxiety about the possibility of prostate cancer is another common reason why repeat prostate biopsies are performed.

OPTIMISING REPEAT BIOPSY PROCEDURE

Timing

The optimal timing of a repeat biopsy procedure is not known and depends among other factors on the outcome of the initial biopsy (e.g. presence of ASAP) and the estimated risk of prostate cancer depending on e.g. rising PSA levels and/or suspicious DRE [8,10]. The later the repeat biopsy is done, the higher the detection rate [8].

Location and number of biopsy cores

Repeat biopsy procedures should consist of extended biopsy schemes designed to sample the areas of the prostate incompletely sampled by the initial biopsy [10]. They should additionally target those areas of the prostate where malignancy is more likely to reside. Repeat extended biopsy schemes may consist of the classic sextant biopsy pattern (sampling the base and apex of the peripheral gland) plus various combinations of anteriorly directed biopsies sampling the transition zone, posterolateral sampling (including the anterior horn of the peripheral zone), and anterior apical biopsies [1,10–12]. The number of cores taken may be guided by prostate volume measured by TRUS [2]. MRI may aid in investigating the possibility of an anterior located tumour, and TRUS or MRI-guided biopsies of the suspicious area may thereafter be performed [8].

One of the most aggressive biopsy approaches is the saturation biopsy technique, which is a multicore biopsy strategy taking ≥20 cores performed under general or local anaesthesia [2]. Local anaesthesia allows the saturation biopsy to be performed in the office setting and should preferably consist of a US-guided peri-prostatic block that can be apical or basal [12]. The assumption of a saturation biopsy is that the cancer is likely to be small and/or located in one of the deeper areas of the prostate. The larger number of evenly distributed samples increases the likelihood of detecting an underlying cancer, regardless of tumour size or location. The exact number of cores required for optimal prostate cancer detection depends on the clinical characteristics of the patient. The role of saturation biopsies for initial biopsies has been shown to be limited, but it may be of value in patients scheduled for a repeat biopsy [1,10]. The prostate cancer detection rate on saturation repeat biopsy ranges from 14 to 43% depending on the number of cores sampled during prior biopsies [3,8,12,13]. Another potential of the saturation biopsy may be to predict more accurately the significance of the cancer, thereby facilitating the selection of men suitable for active surveillance [1,14]. The risk of complications with saturation biopsies appears to be equivalent to biopsy schemes using fewer cores [14].

OPTIMISING REPEAT BIOPSY DECISIONS

PCA3

There has been an extensive search for biomarkers that could aid in the diagnosis of prostate cancer to prevent unnecessary and uncomfortable (repeat) biopsy procedures. One of these new markers is PCA3, a non-coding mRNA that is highly over-expressed (median 66-fold) in >95% of malignant prostate tissue compared with benign and normal prostate tissue [15,16]. The PROGENSA™ PCA3 Assay measures PCA3 and PSA mRNA concentrations in

urine samples taken after a DRE. The PCA3 Score is then calculated as [PCA3 mRNA]/[PSA mRNA]*1000 [17]. Informative rates have shown to range from 94 to 99%, showing that the test is robust and patients rarely have to be retested [18–21]. The PCA3 Score has been shown to be independent of prostate volume, PSA level, number of previous biopsies and age [18,20,21].

Several studies have evaluated the clinical utility of the PCA3 Assay in guiding repeat prostate biopsy decisions [18–21]. In addition, the value of the PCA3 Score in predicting future repeat biopsy outcome is attracting interest [21,22].

Guiding repeat biopsy decisions

A European, prospective multicentre study evaluated the clinical utility of the PROGENSA™ PCA3 Assay in 463 men with one or two prior negative biopsies scheduled for repeat biopsy [18]. In all, 28% of men had a positive repeat biopsy; the higher the PCA3 Score, the greater the probability of a positive repeat biopsy. The mean and median PCA3 Scores were higher in men with a positive repeat biopsy vs a negative repeat biopsy (Fig. 1). The PCA3 Score had a greater diagnostic accuracy for predicting repeat biopsy outcome than %free PSA ([free PSA/total PSA] × 100). The results of that study were consistent with those of a study in 233 North American men with elevated serum PSA levels (≥2.5 ng/mL) and at least one prior negative biopsy of whom 27% had a positive repeat biopsy [19]. Also here the probability of a positive repeat biopsy increased with higher PCA3 Scores. Receiver operating characteristic (ROC) curve analysis showed a statistically significantly higher area under the curve (AUC) for PCA3 (0.68) than for serum PSA (0.52; $P = 0.008$) [19]. Recently, the clinical utility of the PROGENSA™ PCA3 Assay in predicting repeat biopsy outcome was assessed and confirmed in an analysis of the landmark REduction by DUtasteride of prostate Cancer Events (REDUCE) trial [21]. This was a 4-year, randomised, placebo-controlled trial evaluating the effect of the 5α-reductase inhibitor dutasteride on prostate cancer risk in men with total serum PSA levels of 2.5–10 ng/mL and a negative biopsy. Men received a repeat biopsy after 2 and 4 years of follow-up. The PCA3 Assay was used in 1140 men receiving placebo. In all, 18% of these men had a positive repeat biopsy; the probability of a positive repeat biopsy increased with increasing PCA3 Scores from 6% at a PCA3 Score of <5 to 57% at a PCA3 Score of >100. The ROC AUC for predicting repeat biopsy outcome was statistically significantly higher for PCA3 (0.693) than for total serum PSA (0.612; $P = 0.008$). The median PCA3 Score was 17 in men with a negative biopsy and 34 in men with a positive biopsy, which is consistent with the median PCA3 Scores in the European repeat biopsy study (Fig. 1) [18].

FIG. 1. The PCA3 Score is higher in men with a positive biopsy than in men with a negative biopsy [18,21].

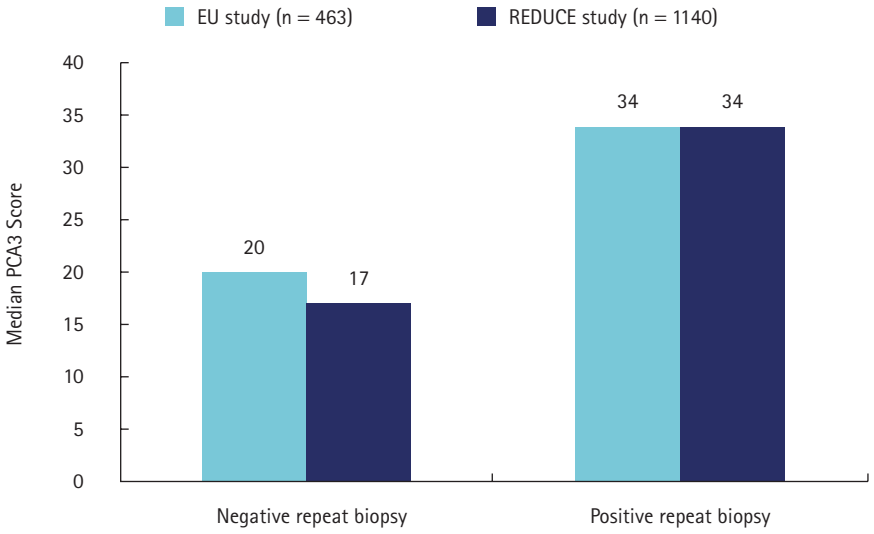

TABLE 2 In univariate analysis the PCA3 Score is a significant and independent predictor of prostate cancer risk and in multivariate analysis the PCA3 Score significantly increased the predictive accuracy of the base model [18]. Reprinted from Eur Urol 2008; 54: 1081–8 (Haese A, de la Taille A, Van Poppel H et al. *Clinical utility of the PCA3 urine assay in European men scheduled for repeat biopsy) with permission from Elsevier*

	Univariate analysis			Multivariate analysis			
				Base model		Base model + PCA3 Score	
	OR	*P*	PA (%)	OR	*P*	OR	*P*
Age	1.051	0.004	0.578	1.042	0.035	1.024	0.243
Serum total PSA	1.063	0.001	0.600	1.07	0.003	1.064	0.007
%free PSA	0.974	0.063	0.578	0.992	0.637	0.988	0.477
DRE	2.610	<0.001	0.577	2.473	0.001	2.263	0.006
Prostate volume	0.990	0.024	0.563	0.982	0.002	0.985	0.015
PCA3 Score		<0.001	0.663				0.006
PA (%)				66.8		71.0	
Increment in PA (%)				+4.2			
P value				<0.001			

OR, odds ratio; PA, predictive accuracy.

Thus, these studies show that the PCA3 Score predicts the probability of a positive repeat biopsy outcome. However, a novel marker should not only show that it predicts prostate cancer risk and improves diagnostic accuracy but it should also increase the combined multivariate predictive accuracy of established risk factors. Several studies reported that PCA3 is a significant and independent predictor of repeat biopsy outcome in univariate analysis (Table 2) [18,21,23]. Importantly inclusion of PCA3 (as a continuous variable or at a specified

threshold) into multivariable models (including e.g. age, serum total PSA, %free PSA, DRE outcome, prostate volume) significantly increased the predictive accuracy of these models [18,20,23]. In the European repeat biopsy study the inclusion of PCA3 into a multivariable model increased its predictive accuracy by up to 4.2% (Table 2) [18]. The REDUCE trial showed that the AUC ROC for a multivariate model including the PCA3 Score and other prostate cancer risk factors (age, family history, prostate volume, total PSA and %free PSA) was 0.753, which was statistically significantly higher compared with the same model without PCA3 (0.717; $P < 0.001$) [21]. The PCA3 Score has also been incorporated in the Prostate Cancer Prevention Trial (PCPT) risk calculator, which combines PSA, DRE, family history, biopsy history, age and race to determine the risk of prostate cancer for individual men [24]. The AUC ROC of the PCPT risk calculator incorporating PCA3 (0.696) was statistically significantly higher than that of the original PCPT risk calculator (0.653; $P < 0.05$). These results confirm that PCA3 can be used in combination with other clinical information to help guide prostate biopsy decisions.

Although the PCA3 Score is a continuous variable, for clinical practice it seems practical to establish threshold values for guiding repeat biopsy decisions. Both the USA and European repeat biopsy studies indicated that a PCA3 Score threshold of 35 provided an optimal balance between sensitivity (47–58%) and specificity (72%) for detecting prostate cancer [18,19]. However, it was also shown that at a PCA3 Score threshold of 35, 67% of biopsies would have been avoided while 21% of Gleason score 7–9 cancers would have been missed [18]. On the other hand, if the PCA3 Score threshold were to be lowered to 20, this would reduce the number of repeat biopsies by 44% while missing only 9% of Gleason score 7–8 cancers. Interestingly, the median PCA3 Scores in men with a repeat negative biopsy were also ≈20 [18,21]. A PCA3 Score threshold of 20 may thus be considered for use in clinical practice to select men in whom repeat biopsy can be avoided.

Predicting future biopsy outcome

The REDUCE study also showed that the PCA3 Score may be predictive of future biopsy outcome [21]. The PCA3 Score at 2 years of follow-up was a significant predictor of biopsy outcome at 4 years of follow-up (AUC ROC 0.634; $P < 0.001$) while serum PSA level (AUC ROC 0.535; $P = 0.328$) and %free PSA (AUC ROC 0.519; $P = 0.678$) were not predictive. Men with a negative repeat biopsy at 2 years and a PCA3 Score of >35 had a two-fold increased risk of a positive biopsy at 4 years ($P = 0.019$). A follow-up study of 51 men with an elevated PCA3 Score (≥20) and a negative repeat biopsy in the European repeat biopsy study has also suggested that the PCA3 Score may predict future biopsy outcome [18,22]. In all, 55% of these men had a positive follow-up biopsy, which is substantially higher than reported for men having a repeat biopsy (10–35%) [1,2,22]. In addition, the PCA3 Score was statistically significantly higher in men with a positive follow-up biopsy vs a negative biopsy (median PCA3 Score 50.4 vs 28.2). This reinforces the hypothesis that a high PCA3 Score in men with a current negative repeat biopsy may predict a future positive repeat biopsy. PCA3 may be detecting cancers that were missed by biopsy or PCA3 may be related to precancerous states that progress. In clinical practice this would mean that in men with a negative biopsy but high PCA3 Score close follow-up is needed.

CONCLUSIONS

In clinical practice there is often the dilemma whether or not to repeat a prostate biopsy. Optimising repeat biopsy procedures, such as adequately sampling prostate areas that were not sampled at a prior biopsy or the use of MRI-guided biopsy, may increase the probability of a positive repeat biopsy. In addition, the use of diagnostic markers such as PCA3 may help physicians and their patients in making better decisions whether to repeat a biopsy. When used in combination with clinical variables such as PSA, age, and family history, the PCA3 Score may help decide whether a repeat biopsy is indicated or can be delayed or avoided and as such reduce the number of unnecessary uncomfortable biopsies. Moreover, the PCA3 Score may be predictive of future biopsy outcome and indicate in which men a close follow-up is needed. The predictive value of the PCA3 Score for future biopsy outcome needs to be further evaluated. Further research should also be directed towards establishing meaningful PCA3 Score thresholds for guiding repeat biopsy decisions in clinical practice. Currently, it seems that a man with a PCA3 Score of <20 can be considered at low risk of harbouring clinically significant prostate cancer and repeat biopsy can be avoided whereas a man with a PCA3 Score of >50 is at high risk of having (significant) prostate cancer and repeat biopsy is indicated.

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CONFLICT OF INTEREST

None declared.

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Abbreviations: **ASAP**, atypical small acinar proliferation; **US**, ultrasound/ultrasonography; **PCA3**, Prostate CAncer gene 3; **NCCN**, The National Comprehensive Cancer Network; **ROC**, Receiver operating characteristic (curve); **AUC**, area under the curve; **REDUCE**, REduction by DUtasteride of prostate Cancer Events (trial); **PCPT**, Prostate Cancer Prevention Trial.