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The Value of an Extensive Transrectal Repeat Biopsy with Anterior Sampling in Men on Active Surveillance for Low-risk Prostate Cancer: A Comparison from the Randomised Study of Active Monitoring in Sweden (SAMS)

Ola Bratt[a,*], *Erik Holmberg*[b], *Ove Andrén*[c], *Stefan Carlsson*[d], *Linda Drevin*[e], *Eva Johansson*[f], *Andreas Josefsson*[a], *Maria Nyberg*[g], *Jonas Sandberg*[h], *Pär Stattin*[i], *David Robinsson*[j]

[a] *Department of Urology, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden;* [b] *Regional Cancer Centre, Västra Götaland, Sahlgrenska University Hospital, Gothenburg, Gothenburg, Sweden;* [c] *Department of Urology, Örebro University Hospital, Örebro, Sweden;* [d] *Section of Urology, Department of Molecular Medicine and Surgery, Karolinska Institute, Stockholm, Sweden;* [e] *Regional Cancer Centre, Uppsala-Örebro, Uppsala, Sweden;* [f] *Department of Urology, Academic Hospital, Uppsala, Sweden;* [g] *Department of Urology, Sahlgrenska University Hospital, Gothenburg, Sweden;* [h] *Department of Urology, Norrland University Hospital, Umeå, Sweden;* [i] *Department of Surgical Sciences, Uppsala University, Uppsala, Sweden;* [j] *Department of Urology, Department of Urology, Jönköping County, Sweden*

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Abstract

Background: A systematic repeat biopsy is recommended for men starting on active surveillance for prostate cancer, but the optimal number and distribution of cores are unknown.
Objective: To evaluate an extensive repeat transrectal biopsy with anterior sampling in men starting on active surveillance.
Design, setting, and participants: Randomised multicentre trial. From 2012 to 2016, 340 Swedish men, aged 40–75 yr, with recently diagnosed low-volume Gleason grade group 1 prostate cancer were included.
Intervention: Either an extensive transrectal biopsy with anterior sampling (median 19 cores) or a standard transrectal biopsy (median 12 cores).
Outcome measurements and statistical analysis: Primary outcome measure: Gleason grade group $\geq$2 cancer. Secondary outcomes: Cancer in anteriorly directed biopsy cores and postbiopsy infection. Nonparametric statistical tests were applied.
Results and limitations: Gleason grade group $\geq$2 cancer was detected in 16% of 156 men who had an extensive biopsy and in 10% of 164 men who had a standard biopsy, a 5.7% difference (95% confidence interval [CI]–0.2% to 13%, $p = 0.09$). There was a strong linear association between prostate-specific antigen (PSA) density and cancer in the anteriorly directed biopsy cores. The odds ratios for cancer in the anteriorly directed cores were for any cancer 2.2 (95% CI 1.3–3.9, $p = 0.004$) and for Gleason grade group $\geq$2 cancer 2.3 (95% CI 1.2–4.4, $p = 0.015$) per 0.1-ng/ml/cm^3 increments. Postbiopsy infections were equally common in the two groups. A limitation is that magnetic resonance imaging was not used.
Conclusions: The trial did not support general use of the extensive transrectal repeat biopsy template, but cancer in the anteriorly directed cores was common, particularly in

* Corresponding author. Department of Urology, Sahlgrenska Academy, University of Gothenburg, SE-413 45 Göteborg, Sweden. Tel. +46 276 3233.
E-mail address: ola.bratt@vgregion.se (O. Bratt).

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men with high PSA density. The higher the PSA density, the stronger the reason to include anterior sampling at a systematic repeat biopsy.
Patient summary: This trial compared two different templates for transrectal prostate biopsy in men starting on active surveillance for low-risk prostate cancer. Cancer was often found in the front part of the prostate, which is not sampled on a standard prostate biopsy.

1. Introduction

Active surveillance is an established method for reducing overtreatment of men with low-grade prostate cancer while maintaining the window of cure [1], but the evidence is poor for how surveillance is best executed. Repeating the systematic biopsies is considered essential [1], but the guidelines' recommendations on the number of biopsy cores and on which parts of the prostate to sample are not based on randomised trials. Several studies have identified the anterior part of the prostate as the most common site for undetected high-grade cancer in men on active surveillance [2–4]. Despite this, none of the current surveillance protocols includes anteriorly directed biopsy cores [5].

The Study of Active Monitoring in Sweden (SAMS) is a randomised clinical trial that compares a standard protocol for active surveillance with an experimental protocol, in which the initial repeat transrectal biopsy (the "confirmation biopsy") is more extensive and the subsequent follow-up is less frequent [6]. The primary endpoint is active treatment within 5 yr. We now analysed the outcome of the initial repeat biopsy in the two study groups to assess the value of the extensive biopsy template with anterior sampling.

2. Patients and methods

SAMS is a prospective multicentre trial with two parts: the randomised SAMS-FU (ISRCTN64891728) and the observational SAMS-ObsQoL [6]. The SAMS-FU trial was planned to test the hypothesis that the follow-up after an extensive initial repeat biopsy can be less intensive than after a standard repeat biopsy. The primary endpoint of the SAMS-FU trial is treatment within 5 yr. The trial recruited patients at 18 Swedish centres between January 2012 and December 2016. We now analysed the outcome of the initial repeat biopsy in the randomised SAMS-FU trial. The SAMS trial was approved by the Regional Ethical Review Board at Lund University (EPN 2010/598).

SAMS-FU included men aged 40–75 yr with a low-volume Gleason grade group 1 prostate cancer, diagnosed within the past 6 mo. Specific inclusion and exclusion criteria are listed in Table 1. The men were randomly allocated (1:1) according to the minimisation method by a two-factor authentication Web-based application, ensuring allocation concealment, to receive either an extensive repeat biopsy with anterior sampling (Group A) or a standard repeat biopsy without anterior sampling (Group B). The randomisation software minimised the imbalance between the number of patients in each group over the stratification variables age ($<$ vs $\geq$65 yr) and local tumour stage (T1c vs T2a).

The protocol specified that the repeat biopsy should be done within 3 mo from randomisation. Per oral antibiotic prophylaxis was given according to local routines, most commonly a single 750-mg dose of ciprofloxacin [7]. All biopsies were taken transrectally in local anaesthesia. A side- or end-fire probe was used according to the urologists' personal preferences. A schematic drawing in the study protocol and synopsis illustrated the intended biopsy locations (Supplementary Fig. 1). The number of biopsy cores depended on the prostate volume.

Extensive biopsy template (Group A). Prostate volume $<$30 cm^3: eight lateral and two medial posterior cores, plus four para-median anteriorly directed cores. Prostate volume 30–59 cm^3: 10 lateral and four medial posterior cores, plus four para-median anteriorly directed cores. Prostate volume 60–89 cm^3: 12 lateral and four medial posterior cores, plus six para-median anteriorly directed cores. The tip of the anteriorly directed biopsies should reach the anterior capsule (Fig. 1). One or two additional cores from previous cancer locations were recommended.

Standard biopsy template (Group B). Lateral posterior cores only. Prostate volume $<$30 cm^3: eight cores. Prostate volume 30–59 cm^3: 10 cores. Prostate volume 60–89 cm^3: 12 cores. One or two additional cores from cancer previous locations were recommended.

The primary outcome measure of this analysis was detection of Gleason grade group $\geq$2 (Gleason score $\geq$7) cancer. Secondary outcome measures were cancer detection in the anteriorly directed biopsy cores and postbiopsy infection. We also analysed the influence of prostate-specific antigen (PSA) density on cancer detection. No other potential explanatory variable was analysed. The histology reports were retrieved for all men who had cancer in the anteriorly directed biopsies, but the specimens were not centrally reviewed.

The proportions of men prescribed antibiotics and/or had an in-patient episode for a urinary tract infection or sepsis within 30 d from the initial repeat biopsy were analysed using data from PCBaSe [8]. Prescriptions of antibiotics relevant for urinary tract infections were extracted from the National Prescribed Drug Registry and relevant discharge diagnoses codes from the National In-Patient Register, similar to a previous nationwide study of postbiopsy infections [9].

Table 1 – Inclusion and exclusion criteria

Inclusion criteria
• Peripheral zone prostate cancer diagnosed in the past 6 mo
• Gleason grade group 1 (Gleason score $\leq$6)
• Maximum 33% of cores with cancer (of 6 to 12 cores)
• Maximum 6-mm cancer in a single core
• Local cancer stage T1c or T2a
• PSA $<$13 ng/ml
• PSA density $<$0.2 μg/l/cm^3
• Prostate volume $<$90 cm^3
• Local therapy with curative intent planned on progression
Exclusion criteria
• Cancer in biopsy cores specifically sampling the anterior prostate
• Any Gleason pattern 4 or 5
• Cancer diagnosed at TUR-P
• Evidence of metastatic cancer
• Any previous therapy for prostate cancer
• 5-α-Reductase inhibitor treatment in the past 12 mo
• Prostate biopsy in the past 12 mo before diagnosis
• Recurrent urinary tract infection or bacterial prostatitis

PSA = prostate-specific antigen.
TUR-P = transurethral resection of the prostate

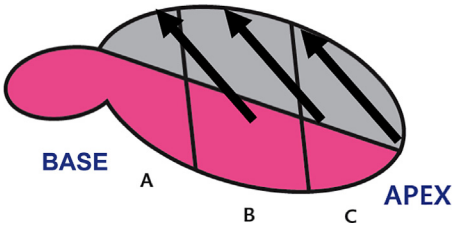

Fig. 1 – Sampling of the anterior prostate in Group A. The investigators were instructed to insert the biopsy needle a bit into the prostate before firing off, so the tip of the biopsy could reach the anterior capsule (black arrows).

2.1. Statistical analysis

The statistical power calculation for the SAMS-FU trial was based on the primary endpoint; no specific power calculation was done for any of the secondary endpoints, such as biopsy findings. We analysed the biopsy findings according to both the allocation (intention to treat) and the actual biopsy template (per protocol). The results from the intention-to-treat analysis are reported in detail, whereas the per-protocol analysis is just briefly summarised. Differences in proportions between the two study groups were compared with one-sided Fisher exact test, and differences in continuous variables within group A with two-sided Mann–Whitney *U* test. Logistic regression was used to model the probability of cancer in the anteriorly directed biopsy cores with PSA density as independent covariate. The predicted probability was graphed by different values of PSA density. Confidence intervals (CIs) were calculated for the proportions.

3. Results

3.1. Number of participants and their clinical characteristics

A total of 340 men were randomised, 170 to each group. In Group A (extensive repeat biopsy with anterior sampling), 14 men had incomplete documentation on biopsy results, leaving 156 for the present analysis. In Group B (standard repeat biopsy), six men had incomplete documentation, leaving 164 for analysis. The baseline clinical characteristics of the men are summarised in Table 2.

The repeat biopsy was done within 6 mo after the diagnostic biopsy in 86% of the men and between 6 and 9 mo after the diagnosis in 14%, with no difference between the groups. The median number of biopsy cores in Group A was 19 (interquartile range [IQR] 16–20), of which a median of 4 were directed anteriorly (range 4–6). An end-fire probe was used for taking the anteriorly directed cores in 69% of the men in Group A. In Group B the median number of cores was 12 (IQR 11–13).

3.2. Primary outcome measure: Detection of Gleason grade group ≥2 cancer

Gleason grade group ≥2 cancer was detected in 16% of the men who had an extensive repeat biopsy with anterior sampling and in 10% of the men who had a standard repeat biopsy, a 5.7% difference (95% CI–0.2–13%, $p = 0.09$). Almost all of these cancers were Gleason grade group 2; only three in each group (2%) were Gleason grade group 3–5 (Table 3). A separate analysis of the 286 men with T1c cancers gave almost identical results.

3.3. Cancer in the anteriorly directed biopsy cores in Group A, association with PSA density

The histology report was unavailable for eight men, leaving 148 for analysis. Of these, 34% had cancer in the anteriorly directed cores and 6.8% had cancer exclusively in the anterior cores. Gleason grade group 2 cancer was found in the anteriorly directed cores in 9.6% and exclusively there in 5.4% of the men. No Gleason grade group 3–5 cancer was detected by the anterior cores.

Table 2 – Baseline characteristics of the 320 men included in the analysis

	Group A Extensive repeat biopsy (*n* = 156)	Group B Standard repeat biopsy (*n* = 164)
Age at randomisation (yr), median (range)	66 (43–74)	66 (46–74)
PSA (ng/ml), median (IQR)	4.9 (3.6–6.7)	5.1 (3.6–6.2)
Prostate volume (cm^3) median (IQR)	38 (30–50)	42 (32–54)
PSA density ($ng/ml/cm^3$), median (IQR)	0.12 (0.09–0.17)	0.11 (0.09–0.17)
Local T stage, *n* (%)		
T1c	139 (89)	147 (89)
T2a	17 (11)	17 (11)
Cores at diagnostic biopsy, median (IQR)	12 (10–12)	12 (10–12)
Cores with cancer, *n* (%)		
1	90 (58)	92 (57)
2–3	63 (40)	66 (40)
4–5	3 (1.9)	6 (3.7)
Percent biopsy cores with cancer, median (IQR)	10 (8.3–17)	10 (8.3–20)
Unilateral cancer, *n* (%)	128 (82)	129 (78)
Bilateral cancer, *n* (%)	23 (15)	29 (18)
Missing, *n* (%)	5 (3.2)	6 (3.7)
Total biopsy cancer length (mm), median (IQR)	1.5 (1.0–3.0)	2.0 (1.0–4.0)

IQR = interquartile range; PSA = prostate-specific antigen.

Table 3 – Cancer detection on the first repeat biopsy in 320 men with a small Gleason grade group 1 prostate cancer in the randomised SAMS trial

	Group A Extensive repeat biopsy (*N* = 156), *n* (%; 95% CI)	Group B Standard repeat biopsy (*N* = 164), *n* (%; 95% CI)
Benign or GGG 1	131 (84; 77–89%)	147 (90; 84–94)
GGG ≥2 (primary outcome)	25 (16; 11–23%)	17 (10; 6.2–16)
GGG 2	22 (14; 9.0–21%)	14 (8.6; 4.8–14)
GGG 3	2 (1.3; 0.2–4.5%)	3 (1.8; 0.4–5.2)
GGG 4	1 (0.6; 0.0–3.5%)	0 (0; 0.0–2.3)
GGG 5	0 (0; 0.0–2.2%)	0 (0; 0.0–2.3)

CI = confidence interval; GGG = Gleason grade group; SAMS = Study of Active Monitoring in Sweden.

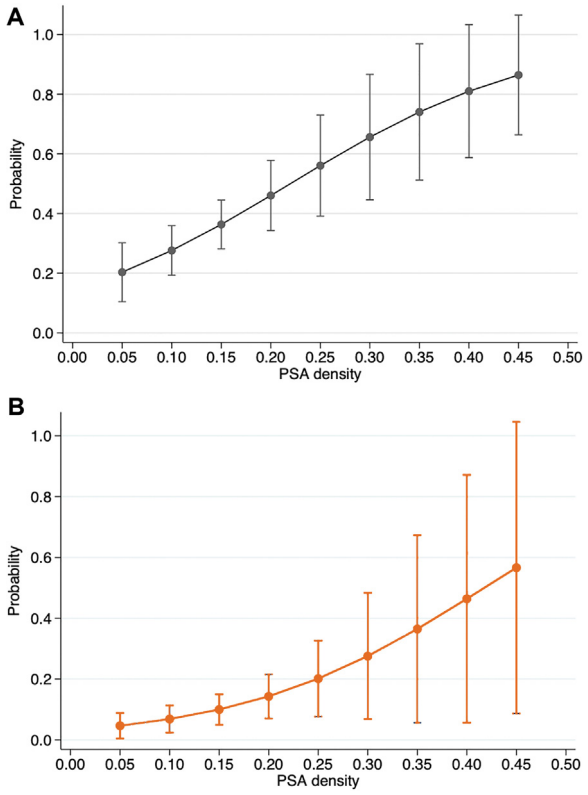

Fig. 2 – (A) Any cancer and (B) Gleason grade group ≥2 cancer in the anteriorly directed cores of the extensive repeat biopsy template among the 148 men with complete histology data in Group A of the Study of Active Monitoring in Sweden (SAMS) trial, plotted against prostate-specific antigen (PSA) density. Vertical bars represent 95% confidence intervals.

There was a strong linear association between PSA density and cancer in the anteriorly directed biopsy cores (Fig. 2A and B). The odds ratios for cancer in the anteriorly directed cores were for any cancer 2.2 (95% CI 1.3–3.9, $p = 0.004$) and for Gleason grade group ≥2 cancer 2.3 (95% CI 1.2–4.4, $p = 0.015$) per 0.1-ng/ml/cm^3 increments.

As many guidelines define the very-low-risk category by PSA density ≥0.15 ng/ml/cm^3, we analysed the proportion of Gleason grade group ≥2 cancer in anteriorly directed cores above and below this arbitrary cut point. Gleason grade group ≥2 cancer was detected in 19% (95% CI 9.3–31%) of 54 men with PSA density ≥0.15 and in 5.3% (95% CI 4.5–17%) of 94 men with PSA density <0.15 ng/ml/cm^3.

3.4. *Postbiopsy infections*

Treatment for infection within 30 d after biopsy was equally common in both groups (10 men in each group). Six men in Group A and five in Group B were admitted to hospital for treatment of infection.

3.5. *Per-protocol analysis*

Six men in the extensive biopsy group had fewer and one man in the standard biopsy group had more biopsy cores taken than the protocol specified. Excluding these in a per-protocol analysis did not change the results. The man in the standard biopsy group who had an extensive biopsy had no cancer in the anteriorly directed cores.

4. Discussion

This is the first randomised trial to report on a comparison between different templates for the repeat biopsy in men starting on active surveillance for low-risk prostate cancer. The trial did not support general use of the extensive transrectal biopsy template. The anteriorly directed biopsy cores did, however, contain cancer in one-third and Gleason grade group ≥2 cancer in one-tenth of the men. PSA density was strongly associated with any and Gleason grade group ≥2 cancer in the anteriorly directed biopsies.

These results confirm previous observations that the anterior prostate is a common location for undetected high-grade cancer in men who start on active surveillance for low-risk prostate cancer, diagnosed on standard transrectal biopsy [2–4]. Taira and co-workers [2] subjected 64 men with low-risk cancer, diagnosed on a standard 12-core transrectal biopsy, to an extensive template-guided trans-perineal biopsy (median 58 cores) in general anaesthesia. Gleason grade group ≥2 cancer was detected in 39% of the men, commonly in the anterior and apical parts of the prostate [2]. This is similar to what has been reported from radical prostatectomy specimens in men who fulfilled active surveillance criteria but chose surgery [2,10,11]. It is thus reasonable to assume that the moderately extensive biopsy template in our study missed a Gleason grade group ≥2

cancer in at least 15% of the men. Routine use of transperineal biopsies in general anaesthesia to detect these remaining 15% of cancers would, however, be very expensive. Moreover, it is probably not necessary to detect every small Gleason grade group 2 cancer; excellent long-term outcome has been reported in men who did not have any extensive transperineal biopsy at the start of active surveillance and therefore were likely to have some undetected Gleason grade group 2 cancer [12,13].

Our results may seem at odds with a report from the Johns Hopkins Hospital on a series of 534 men on active surveillance who had a 14-core transrectal repeat biopsy, with at least two cores from the transition zone [14]. The transition zone cores detected cancer in 16% and Gleason grade group ≥2 cancer in 7% of the men, which is only half of the corresponding proportions in the anteriorly directed cores in our study. The authors concluded that the detection rate was too low to recommend routine transition zone sampling in men on active surveillance. The discrepancy between their and our results may be related to both the number and the location of the biopsy cores. At Johns Hopkins on average only two cores sampled the transition zone, whereas the SAMS protocol specified that four to six cores should reach the anterior capsule of the prostate, which is where most anterior prostate cancers arise [15]. We suggest that the term "transition zone biopsies" is reserved for sampling of the central transition zone and that the term "anterior biopsies" (or "ventral biopsies") is used when the part of the prostate just inside the anterior capsule is sampled.

PSA density is a strong predictor of high-grade prostate cancer, both in men without any known cancer and in men on active surveillance [16,17], but an association between PSA density and anterior high-grade cancer has not been reported previously. The strong association between PSA density and cancer in the anteriorly directed biopsy cores in our study is probably related to the fact that the anterior part of the prostate is the most common location for large and high-grade cancers missed at the diagnostic biopsy [2]. If the PSA density is low, it is unlikely that a large or high-grade cancer is missed; if the PSA density is high, it is likely that such a cancer is missed—and the most likely location of this cancer is in the anterior prostate.

A limitation of our study is that the statistical power to detect a clinically important difference in the detection of Gleason grade group ≥2 cancer was only moderate, as the optimal size of the SAMS trial was calculated based on the primary endpoint, not on secondary endpoints such as biopsy results.

Moreover, in small prostates the standard biopsy might have sampled parts of the anterior prostate, and the anteriorly directed cores of the extensive biopsy might have sampled the posterior prostate; hence, the use of the term "anteriorly directed cores" rather than "anterior cores" in this manuscript. For obtaining biopsy cores that exclusively sample the anterior half of the prostate a transperineal approach is necessary.

The protocol did not specify how to sample suspicious nodules or ultrasound lesions, but as the analysis restricted to T1c cancers gave the same result as the main analysis it is unlikely that this affected the results. A comparison between the recommended number of systematic biopsy cores and the median number of cores that were actually taken suggests that on average two extra cores were taken from previous cancer locations in the standard biopsy group versus only one extra core in the extensive biopsy group. This may have reduced the difference in cancer detection between the two groups.

The external validity of our study is affected by the fact that only men with low-volume cancer were included and that magnetic resonance imaging (MRI) was not used. When the SAMS trial was planned in 2010, the selection of patients for active surveillance was more restrictive than it is now and MRI was rarely used in Sweden for prostate cancer diagnostics. Several studies have since then shown that biopsies targeted to suspicious MRI lesions detect high-grade cancer in a substantial proportion of men on active surveillance [18,19]. Rather surprisingly though, a recent randomised trial reported similar proportions of upgrading by a combination of MRI-targeted and systematic repeat biopsies and by a standard 12-core systematic repeat biopsy in men on active surveillance [19].

The European prostate cancer guidelines now recommend MRI before the first repeat biopsy [1]. Considering the results from our study, it reasonable to include anterior sampling when a systematic biopsy is done after an unsuspicious MRI and in the absence of a prebiopsy MRI, at least in men with a high PSA density (eg, ≥0.15 ng/ml/cm^3). Anterior sampling in these men may affect the decision to start or to continue active surveillance, as this depends on the total cancer and Gleason pattern 4 cancer volumes in the biopsy cores.

5. Conclusions

This randomised trial did not support general use of an extensive transrectal repeat biopsy template with anterior sampling in men who recently started on active surveillance for low-risk prostate cancer. The anteriorly directed biopsy cores did, however, detect cancer in one-third of the men. PSA density was linearly associated with any cancer and with Gleason grade group ≥2 cancer in the anteriorly directed biopsy cores. Anterior sampling should be considered when a systematic prostate biopsy is done in men who wish to start on active surveillance, at least if the PSA density is high (eg, ≥0.15 ng/ml/cm^3).

***Author contributions*:** Ola Bratt has full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Bratt, Holmberg, Andrén, Carlsson, Drevin, Johansson, Josefsson, Nyberg, Sandberg, Stattin, Robinsson.
Acquisition of data: Bratt, Holmberg, Andrén, Carlsson, Johansson, Josefsson, Nyberg, Sandberg, Stattin, Robinsson.
Analysis and interpretation of data: Bratt, Holmberg, Andrén, Carlsson, Drevin, Johansson, Josefsson, Nyberg, Sandberg, Stattin, Robinsson.
Drafting of the manuscript: Bratt.

Critical revision of the manuscript for important intellectual content: Bratt, Holmberg, Andrén, Carlsson, Drevin, Johansson, Josefsson, Nyberg, Sandberg, Stattin, Robinsson.
Statistical analysis: Bratt, Holmberg, Drevin.
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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.eururo.2019.02.035.

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