Prostate Cancer Screening with Magnetic Resonance Imaging: Results from the Second Round of the Göteborg Prostate Cancer Screening 2 Trial

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Abstract

Background: The Göteborg 2 prostate cancer (PC) screening (G2) trial evaluates screening with prostate-specific antigen (PSA) followed by magnetic resonance imaging (MRI) in case of elevated PSA levels.

Objective: To assess the safety of using a 2-yr interval in men who were previously screened positive with PSA but had negative MRI or positive MRI with a negative biopsy.

Design, setting, and participants: A total of 61201 men aged 50–60 yr were randomized and 38366 were invited for screening (years 2015–2020). Men with positive MRI (Prostate Imaging Reporting and Data System [PI-RADS] score ≥3) were scheduled for targeted biopsies. Men with negative MRI or negative biopsies were reinvited after 2 yr. Round 1 and 2 MRI scans (PI-RADS ≥3) of men not diagnosed with PC in round 1 were re-read and classified according to Prostate Cancer Radiological Estimation of Change in Sequential Evaluation (PRECISE) by two radiologists. Interval PCs (detected outside the program before invitation to round 2) were identified by linking to the Regional PC Registry.

Outcome measurements and statistical analysis: Tabulation of overall detection of PC was done. Results and limitations: Between October 2017 and June 2020, 474 men with round 1 elevated PSA and MRI underwent a second screening. Of those, 19% had nonelevated PSA in round 2 and were not examined further. Of the remaining 376 men, 89% had negative MRI. Targeted biopsies yielded 14 PCs: nine grade group (GG) 1 and five GG 2–3. In men with PI-RADS ≥3 and PC diagnosed in round 2, only two (GG 1) progressed according to the PRECISE criteria and the remainder were stable. Ten interval PCs were diagnosed: seven GG 1, one GG 2, and two GG 5. The two GG 5 PCs were PI-RADS 4 and 5 with negative round 1 biopsy.

Conclusions: A 2-yr interval seems to be safe in men with negative MRI, while men with PI-RADS 4 and 5 lesions with negative biopsies should have a closer follow-up.

Patient summary: In prostate cancer screening, a 2-yr follow-up seems to be safe if magnetic resonance imaging did not show highly suspicious findings.

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1. Introduction

Prostate cancer (PC) screening with prostate-specific antigen (PSA) testing followed by systematic biopsies has been shown to decrease PC mortality [1,2] but has not been implemented broadly due to the high risk of overdiagnosis [3–6].

The potential benefit of introducing magnetic resonance imaging (MRI) [7–10] into sequential screening for PC with PSA followed by MRI and changing from systematic to targeted biopsies is mainly to reduce the risk of overdiagnosis [11–13].

A screening program must be balanced; the overall goal is not to diagnose all PCs as early as possible but instead to diagnose them while still curable. Furthermore, the length of the screening interval must be weighed against the risk of interval PCIs to occur and the rate of incurable PCs at rescreening [1,14]. The optimal follow-up interval in screening with PSA followed by MRI has not been established. In previous reports on MRI for diagnostic follow-up of lesions not proven to be cancer, a low risk of PC has been reported at 2-yr follow-up [15,16].

The Göteborg PC screening 2 (G2) trial is an ongoing population-based screening trial with PSA and MRI. The follow-up interval between the first and second rounds is 2 yr in case of elevated PSA and negative MRI or positive MRI with negative biopsies.

One aim of this study was to assess the safety of a 2-yr screening interval when omitting biopsy in men with elevated PSA and negative MRI, or in those with positive MRI and negative targeted biopsies. Another aim was to describe the development of MRI findings from the first to the second screening round, and how these findings were related to the risk of PC in the second round.

2. Patients and methods

2.1. Göteborg PC screening 2 trial design

The G2 trial examines screening for PC with PSA testing followed by MRI in case of elevated PSA. From the population registry, men aged 50–60 yr, living in Göteborg and surrounding counties, were randomized to a screening or a control group. Of men randomized to screening, those who choose to participate were allocated (1:1:1) to one of three study arms. The first arm is the reference arm with a PSA cutoff level of 3 ng/ml (systematic biopsies regardless of MRI findings and targeted biopsies if Prostate Imaging Reporting and Data System [PI-RADS] score ≥3). The second and third arms include only targeted biopsies with PSA cutoff levels of 3 and 1.8 ng/ml, respectively. All participants (and nonresponders) of the first screening round with a PSA value below the cutoff level, or negative MRI, or positive MRI with a negative biopsy were reinvited to a second screening round according to prespecified reinvitation intervals based on PSA. The study protocol is described in detail by Kohestani et al [17], and Figure 1A shows an overview.

Ethical approval by the Ethical Review Board in Gothenburg was obtained in 2015 (DNR 890-14). The trial is registered as ISRCTN94604465.

2.2. Patient cohort

Study participants eligible for this study were men with elevated PSA in the first screening round who underwent MRI but were not diagnosed with PC (Fig. 1A). The final cohort comprised those men who completed the second screening round (Fig. 1B) up to June 30, 2020.

2.3. Specific aims

The aims of this study were the following:

1. To assess the safety of a 2-yr screening interval using the G2 trial screening algorithm; safety was defined as the potential risk of delaying diagnosis from a curable to a noncurable stage
2. To assess the frequency and aggressiveness of PC in the second screening round related to MRI progression evaluated by Prostate Cancer Radiological Estimation of Change in Sequential Evaluation (PRECISE) scores
3. To assess the frequency and aggressiveness of the interval PC between the first and second screening rounds

2.4. MRI protocol

A 3 T MRI scanner (Achieva dStream, Philips Healthcare, Eindhoven, The Netherlands) with a pelvic phased-array surface coil, was used in both
rounds. The imaging protocol was compliant with PI-RADSv2 [18]. In the first round, multiparametric MRI was performed with 0.1 mmol/kg gadolinium-contrast medium (Clariscan, 0.5 mmol/ml; GE Healthcare, Little Chalfont, England). In the second round, biparametric MRI (bpMRI) was performed after April 1, 2019.

2.5. MRI, biopsies, and pathology

Three radiologists with 8, 8, and 9 yr of experience read cases prospectively according to the most current PI-RADS version (v2.1 after 2019) [18]. Each case was read by two readers, and a structured reporting template was completed by the two readers in consensus. MRI-positive lesions (defined as PI-RADS ≥3) were biopsied using a cognitive approach, targeting four cores per lesion. Five urologists (with 5–30 yr of experience) performed the vast majority of these biopsies. A single pathologist specialized in PC (25 yr of experience) assessed all biopsy cores. Men in arm 1 also underwent systematic biopsies irrespective of the MRI findings. In addition, men with negative MRI and PSA 10 ng/ml in arms 2 and 3 underwent systematic biopsies. All men with PC detected with targeted biopsies in arms 2 and 3 were recommended additional 12-core systematic biopsies. Clinically significant PC was defined as PC with a Gleason score of ≥7 (grade group [GG] ≥2) [19,20] in any of the biopsy cores.

For PRECISE [21] scoring, a consensus re-read of the first- and second-round MRI examinations was performed by two of the study radiologists. In the re-read, MRI examinations (both rounds) were assessed according to PI-RADSv2.1 and the risk of MRI progression was scored according to the PRECISE recommendations originally developed for active surveillance. In PRECISE, the likelihood of radiologic progression is scored on a 1–5 scale, where score 1 represents resolution of previous features suspicious on MRI, score 3 represents lesions with stable imaging MRI features, and score 5 represents definitive radiologic stage progression. Men with persistently negative MRI were scored PRECISE 3 in this study. Size was measured as a single measurement of the maximum diameter. Significant size progression was defined as ≥5 mm in any direction measured on the images with best lesion conspicuity [22]. Readers had access to previous biopsy results and PSA. No biopsies were performed based on the results from the re-read.

Fig. 1 – (A) Overview of G2 trial. * Systematic biopsies performed if negative MRI and PSA > 10 ng/ml. In all three study arms, men who completed the first screening round without being diagnosed with PC were reinvited for a second screening after 2 yr. (B) Flow diagram. (C) PCs detected in screening round 2 related to MRI findings in rounds 1 and 2. G2 trial = Göteborg PC screening 2 trial; GG = grade group; ISUP = International Society of Urological Pathology; MRI = magnetic resonance imaging; PC = prostate cancer; PI-RADS = Prostate Imaging Reporting and Data System; PSA = prostate-specific antigen.

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### Table 1 – Patient characteristics

|                        | Overall study population | Men with re-read of MRI |
|------------------------|--------------------------|-------------------------|
| Number of participating men with MRI in rounds 1 and 2, n | 474                      | 104                     |
| Age at PSA round 1 (yr), median (IQR)                  | 59 (56–61)               | 59 (56–61)              |
| PSA at round 1 (ng/ml), median (IQR)                  | 3.2 (2.4–4.3)            | 3.2 (2.2–4.2)           |
| Prostate volume at round 1 (ml), median (IQR)          | 48.0 (39.0–63.0)         | 51.0 (42.0–64.0)        |
| PSA at round 1 (ng/ml²), median (IQR)                  | 0.064 (0.050–0.090)      | 0.061 (0.047–0.081)     |
| Men with biopsies in first round, number (%)           | 172 (36)                 | 85 (82)                 |
| Men with biopsies in second round, number (%)          | 78 (16)                  | 48 (46)                 |
| Screening detected PCs in second round, any ISUP GG, number (%) | 23 (5)                  | 16 (15)                 |
| Screening detected PCs in second round, GG 2–3, number (%) | 5 (1)                   | 5 (5)                   |
| Men with targeted biopsies in second round, number (%) | 36 (8)                   | 36 (35)                 |
| Number of screening detected PCs with targeted biopsy in second round, any GG | 14                      | 14                      |
| Number of screening detected PCs with targeted biopsy in second round, GG 2–3 | 5                      | 5                      |
| Number of screening detected PCs with systematic biopsy only in second round, any GG | 9                      | 2                      |
| Number of screening detected PCs in second round with systematic biopsy only in second round, GG ≥ 2 | 0                      | 0                      |

GG = grade group; IQR = interquartile range; ISUP = International Society of Urological Pathology; MRI = magnetic resonance imaging; PC = prostate cancer; PI-RADS = Prostate Imaging Reporting and Data System; PSA = prostate-specific antigen; PSAD = PSA density.

* Men with positive MRI (PI-RADS ≥3) at least once in round 1 or 2.

### Table 2 – Characteristics of men with interval cancers

| First-round PSA | First-round MRI | First-round biopsies | Risk group | Treatment | Re-read first-round MRI |
|-----------------|-----------------|----------------------|------------|-----------|-------------------------|
| 3.4             | PI-RADS 2       | None                 | GG 1       | AS        | PI-RADS 4               |
| 3.3             | PI-RADS 5       | Benign               | GG 5       | RP        | PI-RADS 5               |
| 3.5             | PI-RADS 2       | None                 | GG 1       | AS        | PI-RADS 4               |
| 4.1             | PI-RADS 4       | Benign               | GG 5       | RP        | PI-RADS 4               |
| 2.1             | PI-RADS 2       | None                 | GG 1       | AS        | PI-RADS 2               |
| 2.9             | PI-RADS 2       | None                 | GG 1       | AS        | PI-RADS 2               |
| 7.7             | PI-RADS 2       | None                 | GG 1       | AS        | PI-RADS 2               |
| 8.8             | PI-RADS 3       | Benign               | GG 2       | AS        | PI-RADS 4               |
| 3.1             | PI-RADS 2       | None                 | GG 1       | AS        | PI-RADS 2               |

AS = active surveillance; GG = grade group; MRI = magnetic resonance imaging; PC = prostate cancer; PI-RADS = Prostate Imaging Reporting and Data System; PSA = prostate-specific antigen; RP = radical prostatectomy.

* Out of 695 men who underwent first-round MRI examinations and had PC detected outside the study before invitation to second round.

#### 2.6. Interval cancer

Interval PCs were identified by linking with the Regional PC Registry. In this study, all men diagnosed with PC after completion of the first screening round with negative results but before participating in the second screening round were considered to have interval cancer. After completion of the first round, a total of 697 men were considered at risk of developing interval PC (Fig. 1). The last date of data linkage was September 25, 2020.

#### 2.7. Statistical analysis

All analyses were descriptive, with results presented as frequencies and percentages. The statistical analyses were carried out using the SPSS version 26.0: IBM Corp., Armonk, NY, USA.

#### 3. Results

##### 3.1. MRI outcome round 2

The final study cohort consisted of 474 men with elevated PSA who had completed screening round 1 with either negative MRI or positive MRI with negative biopsies, and had undergone a 2-yr follow-up screening. Of these men, 383 (81%) had persistently elevated PSA and were eligible for follow-up MRI. In seven of 383 (2%) men, MRI was not performed or incomplete, resulting in 376 men examined with MRI in round 2 (Fig. 1B). Of them, 335 (89%) were scored MRI negative. A total of 104 men had positive MRI in either round 1 (n = 63) or round 2 (n = 19), or both rounds (n = 22; Fig. 1C). Baseline characteristics of the 474 men and the 104 men with re-read of MRI examinations are shown in Table 1.
21 biopsies in men. The prostate imaging reporting and data system (PI-RADS) score of nine stable PCs was determined using PI-RADS 1–5. GG = grade group; MRI = magnetic resonance imaging; PC = prostate cancer; PI-RADS = Prostate Imaging Reporting and Data System; PRECISE = Prostate Cancer Radiological Estimation of Change in Sequential Evaluation.

### 3.2. Biopsy outcome round 2

In round 2, targeted biopsies were performed in 36/41 (88%) of MRI-positive men yielding a total of 14 PCs, out of which nine were GG 1, four were GG 2, and one was GG 3. In five men, targeted biopsies were deferred after shared decision-making. Another nine PCs (all GG 1) were detected among men in arm 1 with systematic biopsies only. Seven of these men were MRI negative in both rounds.

### 3.3. Interval cancers

Out of ten men with interval cancer, none had clinical PC symptoms at diagnosis (Table 2). Two men had high-risk PCs (GG 5); both were MRI positive in round 1 (one PI-RADS 4 and one PI-RADS 5, both had peripheral zone PC located dorsally in the right apex and the left base, respectively) but with negative targeted biopsies (biopsy failures). In addition, one man with a PI-RADS 3 lesion and benign targeted biopsies was diagnosed with GG 2 PC (2 mm Gleason 4 cancer core length) at systematic biopsies outside the study. All the remaining seven men had low-risk PC (GG 1). A review of MRI examinations in these seven men resulted in a not previously reported PI-RADS 3–4 lesion in three men. All GG 1–2 interval PCs were managed with active surveillance.

### 3.4. PRECISE scoring

Table 3 shows the results of retrospective PRECISE scoring of men with positive MRI at least once and the number of detected PCs with targeted biopsies in round 2.

|                | PRECISE 1 | PRECISE 2 | PRECISE 3 | PRECISE 4 | PRECISE 5 | Total |
|----------------|-----------|-----------|-----------|-----------|-----------|-------|
| PI-RADS ≤2     | 0         | 5         | 47        | 7         | 0         | 59    |
| PI-RADS 3      | 0         | 1         | 9         | 0         | 0         | 10    |
| PI-RADS 4      | 1         | 15        | 18        | 1         | 0         | 35    |
| PI-RADS 5      | 0         | 0         | 0         | 0         | 0         | 0     |
| Total          | 1         | 21        | 74        | 8         | 0         | 104   |

In men with progressing PRECISE 4 lesions, two GG 1 PCs were detected.

### 4. Discussion

This study shows that the risk of significant PC diagnosed during the 2 yr after the first screening (interval cancer) and at repeat screening was low. However, the risk was higher in men with positive first-round MRI but with a negative biopsy (five out of 85) compared with men with negative first-round MRI (three of 291; Table 2 and Fig. 1C).

In the group of men with negative first-round MRI, a vast majority (93%) were negative also at 2-yr follow-up. Among these men, a small number of low-risk (GG 1) PCs were detected, in all cases by systematic biopsies routinely performed in case of negative MRI in the first study arm and in case of PSA > 10 ng/ml in arms 2 and 3. Furthermore, only seven interval cancers, all managed with active surveillance, were diagnosed among men with negative first-round MRI.

A certain number of PCs prevalent in the first round in arms 2 and 3 are expected to remain undetected since men in these two study arms with elevated PSA and negative MRI examinations were not biopsied. However, our results indicate that the rate of aggressive PC is very low in men with negative MRI, at least in this population of relatively young men (median age 59 yr). These data further suggest that a longer interval may be used if other risk factors, such as PSA, are low. The next scheduled screening of men with negative second-round MRI after 4yr will clarify this. Considering that nine out of ten men continued to have negative MRI at second-round screening, such an extended interval, if safe, would save a lot of resources.

High-risk interval PCs were diagnosed in two men with first-round PI-RADS 4 and 5 lesions but a negative biopsy. Another GG 2 PC was detected in a man with positive MRI but a negative biopsy. Even though these figures are still low compared with the total number of high-risk PCs detected during round 1 (n = 20, data not shown), our results indicate that biopsy failures are more common than MRI failures in missing the high-risk cancers, at least in the context of how...
our study was designed. We used cognitive targeted biopsies via the transrectal approach, in which all urologists in this study have a lot of experience. However, it is well known that PCs, especially those located anteriorly in large glands, are sometimes difficult to reach [23]. Changing to a perineal approach with, or without, a fusion technique may improve this, even if randomized studies comparing cognitive and fusion-directed biopsies have not demonstrated a clear benefit [24]. A more important consideration is that in men with highly suspicious MRI findings and negative biopsies, a 2-yr interval is probably too long. A rebiopsy of these men (constituting of roughly one in ten men under the risk of being diagnosed with interval PC in this study) within 3–6 mo with an extended number of cores and possibly a fusion technique should be considered. The study protocol was amended in 2020, requiring men with PI-RADS 5 lesions and negative biopsies to be discussed at a clinical MRI conference, and these men were reinvited after 3 mo for new targeted biopsies. Larger PI-RADS 4 lesions with clearly restricted diffusion should also be considered for early rebiopsy.

The re-reading of MRI in men with at least one positive MRI finding yielded some interesting results. The frequency of MRI progression was low (8%), compared with active surveillance cohorts [25,26], and no cases showed stage progression. Furthermore, only low-risk PC was detected in progressing lesions. Our results support the previously reported high sensitivity of MRI to detect clinically significant PC [7]: the few first-round PCs left undiagnosed appear to have a low potential of progression. The risk of progressing PC due to diagnostic error—MRI or biopsy failure—was also low. Except for the two high-risk interval cancers, the five PCs (four GG 2 and one GG 3) detected in the second round did not progress. Two of these cases were considered biopsy failures (first-round MRI positive) and three were considered MRI failures (first-round MRI negative but retrospectively scored positive).

This study has strengths and limitations. The major strengths are the population-based randomized design and the size of the study cohort. The consensus reading with two experienced radiologists in the field is another strength but may also be a limitation, as this is not the standard in everyday practice. The relatively limited age span among participants at randomization is a limitation. Whether these results will be replicable in older men is so far unknown. In the second screening round, only bpMRI was used. However, the same scanner, diffusion-weighted imaging protocol, and readers were used in both rounds, and we have previously shown that PC detection in screening is noninferior with bpMRI to that with multiparametric MRI [27]. It could be discussed whether grading risk of MRI progression according to PRECISE is valid as it was developed for active surveillance and not for a screening cohort of men with MRI lesions not proved to be cancer. If a lot of PCs were left undiagnosed, we would have expected—at least in a subset of the population—a higher frequency of progression similar to that of a cohort of men managed by active surveillance. That none had progression according to PRECISE criteria and GG $\geq 2$ PC is an important finding in this study and supports the use of PRECISE also in this type of cohort.

5. Conclusions

The number of intermediate- or high-risk PCs in men with negative first-round MRI was very low in repeat screening, indicating that a 2-yr interval is safe in this group and suggesting that an even longer interval could be feasible.

The number of intermediate- or high-risk PCs in men with positive first-round MRI and a negative biopsy was not negligible, indicating that men with PI-RADS 4 and 5 lesions with a negative biopsy should have a closer follow-up.

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