Role of Magnetic Resonance Imaging in Prostate Cancer Screening: A Pilot Study Within the Göteborg Randomised Screening Trial

Anna Grenabo Bergdahl a,*, Ulrica Wilderäng b, Gunnar Aus c, Sigrid Carlsson a,d, Jan-Erik Damber a, Maria Frånlund a, Kjell Getered e, Ali Khatami a, Andreas Socratous e, Johan Stranne a, Mikael Hellström e, Jonas Hugosson a

a Department of Urology, Institute of Clinical Sciences, Sahlgrenska Academy at University of Gothenburg, Sahlgrenska University Hospital, Gothenburg, Sweden; b Division of Clinical Cancer Epidemiology, Department of Oncology, Institute of Clinical Sciences, Sahlgrenska Academy at University of Gothenburg, Gothenburg, Sweden; c Department of Urology, Carlanderska Hospital, Gothenburg, Sweden; d Department of Surgery (Urology Service), Memorial Sloan-Kettering Cancer Centre, NY, USA; e Department of Radiology, Institute of Clinical Sciences, Sahlgrenska Academy at University of Gothenburg, Sahlgrenska University Hospital, Gothenburg, Sweden

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Abstract

Background: Magnetic resonance imaging (MRI) and targeted biopsies (TB) have shown potential to more accurately detect significant prostate cancer compared with prostate-specific antigen (PSA) and systematic biopsies (SB).

Objective: To compare sequential screening (PSA + MRI) with conventional PSA screening.

Design, setting, and participants: Of 384 attendees in the 10th screening round of the Göteborg randomised screening trial, 124 men, median age 69.5 yr, had a PSA ≥ 1.8 ng/ml and underwent a prebiopsy MRI. Men with suspicious lesions on MRI and/or PSA ≥ 3.0 ng/ml were referred for biopsy. SB was performed blinded to MRI results and TB was performed in men with tumour-suspicious findings on MRI. Three screening strategies were compared (PSA ≥ 3.0 + SB; PSA ≥ 3.0 + MRI + TB and PSA ≥ 1.8 + MRI + TB).

Outcome measurements and statistical analysis: Cancer detection rates, sensitivity, and specificity were calculated per screening strategy and compared using McNemar’s test.

Results and limitations: In total, 28 cases of prostate cancer were detected, of which 20 were diagnosed in biopsy-naïve men. Both PSA ≥ 3.0 + MRI and PSA ≥ 1.8 + MRI significantly increased specificity compared with PSA ≥ 3.0 + SB (0.73 vs. 0.46, p = 0.008). The detection rate of significant cancer was higher with PSA ≥ 1.8 + MRI compared with PSA ≥ 3.0 + MRI (0.92 and 0.79 vs. 0.52; p < 0.002 for both), while sensitivity was significantly higher for PSA ≥ 1.8 + MRI compared with PSA ≥ 3.0 + MRI (0.73 vs. 0.92 and 0.79 vs. 0.52; p < 0.002 for both).

Conclusion: A screening strategy with a lowered PSA cut-off followed by TB in MRI-positive men seems to increase the detection of significant cancers while improving specificity. If replicated, these results may contribute to a paradigm shift in future screening. If replicated, these results may contribute to a paradigm shift in future screening.

Patient summary: Major concerns in prostate-specific antigen screening are overdiagnosis and underdiagnosis. We evaluated whether prostate magnetic resonance imaging could improve the balance of benefits to harm in prostate cancer screening, and we found a promising potential of using magnetic resonance imaging in addition to prostate-specific antigen.
1. Introduction

Prostate-specific antigen (PSA)-based screening has proved effective in reducing prostate cancer (PC)-specific mortality [1,2], but is associated with overdiagnosis of low-malignant cancers, and underdiagnosis of potentially lethal cancers [3,4]. There is a need for a more effective screening strategy that improves upon the benefits in terms of increased sensitivity and reduces harm by avoiding unnecessary biopsies and overdiagnosis.

The current diagnostics for PC (PSA, digital rectal examinations, and systematic transrectal ultrasound (TRUS)-guided biopsy) are far from perfect. Firstly, the specificity of PSA is low, no cut-off value can rule out PC, and only about 25% of men with a PSA 3–10 ng/ml have cancer on TRUS-guided biopsy [2,5,6]. Secondly, the systematic biopsy (SB)-approach is a limitation for diagnostic accuracy. TRUS-guided SBs are upgraded in as much as 35–46% of cases after radical prostatectomy [7–9], with anterior and transition-zone cancers frequently being missed [10]. Overdiagnosis is another problem as 30–60% of men in the ages 50–70 yr 

2. Methods

2.1. Patients

The pilot study was nested within the 10th and last screening round of the Göteborg randomised screening trial, in which 20,000 men aged 50–64 yr were randomised to a screening and a control group in 1995. Men in the screening group received invitations to PSA-screening biennially until an upper age limit (average 69 yr). A PSA > 3.0 ng/ml (corresponding to a PSA of ≥ 2.54 ng/ml if calibrated to the World Health Organisation) was considered an indication for TRUS-guided SB. Controls were not invited. The design of the Göteborg randomised screening trial has been described previously [2].

2.2. MRI

All examinations were performed using a 3Tesla system (Philips Achieva 3.0, Philips Healthcare, Best, the Netherlands). During the first part of the study, a SENSE Cardiovascular Array Coil with 32 overlapping elements was used. During the study period the system was upgraded and a digital coil system (dStream Torso with integrated anterior and posterior coils) was used (no endorectal coil). Three sequences were used: T2-weighted, dynamic contrast-enhanced, and DWI. For DWI, b-values 0–1000 were used. Apparent diffusion coefficient-maps were calculated and qualitatively assessed. MR-spectroscopy was not performed. Suspicious lesions were pointed out in a diagram by region in the transversal and sagittal plane and scored according to the validated Prostate Imaging Reporting and Data System for each sequence, ranging from 1 to 5 according to the likelihood of significant PC presence [16,19–21]. A score in any sequence of ≥ 3 (equivocal) was regarded as positive. All images were read in consensus by three radiologists of whom two had several years’ experience of MRI-reading.

2.3. Study algorithm

Men with PSA ≥ 1.8 ng/ml were referred for evaluation with MRI (sequential testing). Men with a positive MRI and/or those with PSA of ≥ 3.0 ng/ml were referred for biopsy at a second visit. One urologist (J.H.) performed all biopsies. The 10-core TRUS-guided SB was sampled first, blinded to MRI results, using a scheme with 12 anterior and 12 posterior sectors of which 10 posterior were sampled routinely. The MRI results were then revealed, and MRI-targeted biopsy (TB) was performed on men with cancer-suspicious findings on MRI through three additional cores sampled per suspicious region by means of “cognitive” targeting. Men with negative MRIs and a PSA < 3.0 ng/ml were assumed cancer-free and released without further work-up.

Through this algorithm, three different screening strategies were identified:

1. PSA ≥ 3.0 ng/ml followed by SB (“reference strategy”)
2. PSA ≥ 3.0 ng/ml + MRI followed by TB in MRI-positive men (no SB)
3. PSA ≥ 1.8 ng/ml + MRI followed by TB in MRI-positive men (no SB)

Each man was defined as screen-positive or screen-negative according to each of these strategies. Similarly, cancers were defined as screen-detected or missed by each respective strategy, including whether detected at SB, TB, or both.

2.4. Classification of cancers

Cancers were classified according to the modified Epstein criteria for clinically insignificant PC (clinical stage [digital rectal examinations only] T1c, PSA density < 0.15, GS < 7, ≤ 2 positive cores, and unilateral cancer) [15,22]. Due to sampling differences between MRI-positive (10 SB + minimum three TB) and MRI-negative men (10 SB), we translated the number of “positive cores” into the number of “positive sectors” in order not to overestimate cancer extent in men who underwent TB.

2.5. Statistics

The main outcome measurement was cancer detection rates, defined as the proportion of men screened that had screen-detected PC according to screening strategy 1, 2, and 3. Strategy 1 was regarded as a reference. We observed a higher MRI-attendance among men with PSA ≥ 3.0 ng/ml than among men with PSA 1.8–2.99 ng/ml. Therefore, in comparison between the screening strategies, we corrected for this imbalance by calculating the cancer yield with Strategy 2 and 3 as if all men with an indication for MRI consequently underwent MRI, followed by TB if indicated. Similarly, we calculated the outcome for Strategy 1 as if all men with an indication for SB actually underwent SB.

Point estimates for the statistics sensitivity, specificity, and positive and negative predictive values were calculated as row or column percentages of the two-by-two tables. The binominal option provided exact confidence intervals. Analyses were made using the free statistical software R, utilizing the package DTComPair [23,24]. A p value for
comparing sensitivities and specificities were calculated with McNemar’s test. A \( p \) value for comparing positive predictive value and negative predicted value were calculated using the method described by Moskowitz and Pepe [25].

The number needed to biopsy to detect one PC was calculated, as well as the number needed to undergo MRI + TB to detect one PC. Biopsy modes were compared (SB vs TB) with regards to cancer yield by using the Z-test for population proportions.

2.6. Ethical committee

The ethical committee at the Göteborg University (approval number: 130408) approved the study.

3. Results

The 10th screening round of the Göteborg screening trial took place during 2013–2014, and of the 596 men invited 384 (64%) attended. The median age was 69.3 yr (interquartile range [IQR] 69.0–69.6) and the median PSA was 1.6 ng/ml (IQR 0.9–2.7). Of the 172 men with a PSA \( \geq 1.8 \) ng/ml (median 2.9, IQR 2.3–3.8), 127 underwent a prebiopsy MRI. In total, one third (42/127) of MRIs were positive, and in almost half (19/40) of those cancer was detected at TB. Nine additional cancers were detected in 56 men undergoing SB only (following a negative MRI or nonattendance at MRI). The overall cancer detection rate was 7.3% (28/384) (Fig. 1).

Of the three screening strategies analysed, the most effective in terms of cancer detection rate was Strategy 3. Compared with the reference, this strategy yielded a 48% higher detection rate of significant PC (5.9% vs 4.0%), and a 38% higher detection rate of GS \( \geq 7 \) PC (3.7% vs 2.6%). The cancer detection rate with Strategy 2 was lower than with the reference. However, Strategy 2 detected the fewest insignificant cancers and was the most efficient in terms of the number needed to biopsy (Tables 1 and 4).

The proportion of men with an indication for biopsy decreased from 20% with the reference strategy to 6.5% with Strategy 2 and 15% with Strategy 3. In absolute numbers, these proportions corresponded to 70 SB with the reference, 20 TB with Strategy 2, and 40 TB with Strategy 3. Of the 40 TBs performed, 35 (88%) only required three cores (corresponding to one MRI-lesion). Apart from the 70 SBs performed in men with PSA \( \geq 3.0 \) ng/ml, another 20 SBs were performed in men with a positive MRI and PSA 1.8–2.99 ng/ml, so, in total, 90 SBs were performed within this study. TB was significantly more effective than SB on a per-patient basis, with a cancer-positivity rate of 48% (19/40) versus 26% (23/90), \( p = 0.014 \) and a cancer-positivity rate for significant PC of 40% (16/40) versus 20% (18/90), \( p = 0.017 \). The cancer-positivity correlating with Prostate Imaging Reporting and Data System 3/4/5 were 37%, 75%, and 100%. Corresponding rates for significant PC were 23%, 75%, and 100% (Table 6).

Seven PCs were detected at TB among men with a positive MRI and PSA 1.8–2.99 ng/ml (Table 2). Three of those were GS 3+4, and, in total, four were significant. In total, seven cancers were not depicted by MRI, of which the majority were low-risk cancers; although two were GS 3+4, and, in total, three were significant (Table 3).
performances of the three screening strategies are given in Figure 2 and Tables 4 and 5.

3.1. Previous biopsy

Attendees in the 10th round were previously screened to a large extent. Only 2.0% were first-time screenees; the remaining 98% were PSA-screened one to nine times before. Of the 90 men referred for biopsy, 57 (63%) were biopsy-naïve and 33 (37%) previously biopsied. Of men attending MRI, 53 were biopsy-naïve and 29 were previously biopsied. The biopsy-naïve were three times more likely to have a positive MRI (64%; 34 of 53 men) than those previously biopsied (21%; six of 29 men). However, the risk that the MRI lesion revealed cancer at TB was similar in biopsy-naïve (47%; 16 cancers found at TB in 34 men) and previously biopsied men (50%; three cancers found at TB in six men).
4. Discussion

There is an urgent need for a better PC-screening strategy that can circumvent the low specificity of PSA. This pilot study shows promising potential of using MRI in screening to identify harmful cancers and minimise unnecessary biopsies. Instead of referring all men with PSA \( \geq 3.0 \text{ ng/ml} \) for SB, sequential screening with MRI as an indication for TB (without SB) in men with PSA \( \geq 1.8 \text{ ng/ml} \) reduced the proportion of men biopsied by 26% while increasing the detection rate of significant cancers by 48% (from 4.0% to 5.9%) and the detection of GS \( \geq 7 \) cancers by 43% (from 2.6% to 3.7%). The full-sized trial, Göteborg-2, has started to further establish the role of MRI in screening for PC.

Imaging with MRI plays two roles in PC-screening. Firstly, it functions as a secondary screening test, exempting men with nonsuspicious tests from biopsy. Sequential screening is a strategy that can increase specificity and, according to the World Health Organisation, is a recommended option in cervical cancer screening [26]. However, sequential testing might jeopardise sensitivity [27]. In this study, MRI reduced the need for biopsy by 68% in men with PSA \( \geq 3.0 \text{ ng/ml} \) (common cut-off for biopsy), but at a cost of lowered sensitivity. PSA \( \geq 3.0 \text{ ng/ml} \) + MRI missed three significant PCs (of which two were GS 3+4 cancers). However, two significant cancers were detected by MRI-TB only in those men (PSA \( \geq 3.0 \text{ ng/ml} \)), while missed by the standard SB approach.

The second function of MRI is to provide an image of the lesion(s) so that sampling can be more precise. In this study, TB was significantly more accurate than SB on a per-patient basis in terms of cancer-positivity rate (48% vs 26%, \( p = 0.014 \)). More importantly, TB outperformed SB in detecting clinically significant PC (40 vs 20%, \( p = 0.017 \)). These findings are in line with several studies showing a greater accuracy of MRI-TB than SB in the diagnosis of PC. Hambrock et al [17] reported a significantly improved overall accuracy of TB (88%) over SB (55%) in determining Gleason grade. Haffner et al [28] demonstrated an overall diagnostic accuracy of 98% with TB versus 88% with SB in biopsy-naïve men referred for prebiopsy MRI, and that TB detected 16% more GS \( \geq 7 \) cancers. Puech et al [29] reported a 67% yield of significant PC with TB versus 52% with SB in 67 men with suspicious prebiopsy MRIs out of 95 men with a clinical suspicion of localised PC.

We analysed three different screening strategies, of which Strategy 2 was the most accurate taking both

### Table 4 – Estimated test performance for prostate cancer detection of three different screening strategies

<table>
<thead>
<tr>
<th></th>
<th>Strategy 1</th>
<th>Strategy 2</th>
<th>Strategy 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1. PSA ( \geq 3 ) (SB)</td>
<td>2. PSA ( \geq 3 + \text{MRI} ) (TB)</td>
<td>3. PSA ( \geq 1.8 + \text{MRI} ) (TB)</td>
</tr>
<tr>
<td></td>
<td>%</td>
<td>95% CI</td>
<td>n</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>0.64</td>
<td>0.47–0.82</td>
<td>0.46</td>
</tr>
<tr>
<td>Specificity</td>
<td>0.52</td>
<td>0.43–0.62</td>
<td>0.92</td>
</tr>
<tr>
<td>PPV</td>
<td>0.27</td>
<td>0.16–0.37</td>
<td>0.60</td>
</tr>
<tr>
<td>NPV</td>
<td>0.84</td>
<td>0.75–0.93</td>
<td>0.87</td>
</tr>
<tr>
<td>NNB per PC</td>
<td>4</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>NNB per sign PC</td>
<td>5</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>NNB per GS ( \geq 7 ) PC</td>
<td>8</td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>NNMRI + TB per PC</td>
<td>–</td>
<td></td>
<td>5</td>
</tr>
<tr>
<td>NNMRI + TB per sign PC</td>
<td>–</td>
<td></td>
<td>6</td>
</tr>
<tr>
<td>NNMRI + TB per GS ( \geq 7 ) PC</td>
<td>–</td>
<td></td>
<td>9</td>
</tr>
</tbody>
</table>

CI = confidence interval; GS = Gleason score; MRI = magnetic resonance imaging; n = number; NNB = number needed to biopsy; NNMRI = number needed to undergo MRI; NPV = negative predictive value; PC = prostate cancer; PPV = positive predictive value; PSA = prostate-specific antigen; TB = targeted biopsy, SB = systematic biopsy, sign = significant.

### Table 5 – Comparison between screening strategies for significant differences

<table>
<thead>
<tr>
<th></th>
<th>Strategy 1 vs 2</th>
<th>Strategy 1 vs 3</th>
<th>Strategy 2 vs 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>0.21</td>
<td>0.47</td>
<td>0.008</td>
</tr>
<tr>
<td>Specificity</td>
<td>&lt;0.001</td>
<td>0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PPV</td>
<td>&lt;0.001</td>
<td>0.006</td>
<td>0.09</td>
</tr>
<tr>
<td>NPV</td>
<td>0.55</td>
<td>0.17</td>
<td>0.03</td>
</tr>
</tbody>
</table>

NPV = negative predictive value; PPV = positive predictive value.
ongoing studies in patients with a clinical suspicion of PC remains to be evaluated. This question is also evaluated in diagnosis but whether it is cost-effective in routine screening unnecessary biopsies and to potentially reduce overdiagnosis. According to our results, MRI can be used to avoid equalled that of standard care but improved quality of life [33].

A new screening strategy for PC involving imaging with MRI appears to be highly accurate in detecting significant cancer and minimising unnecessary biopsies. If verified in the full-sized trial, these pilot results may contribute to a paradigm shift in the approach to early detection of PC.

### Table 6 – Correlation between Prostate Imaging Reporting and Data System score and cancer at the following targeted biopsy in men with positive magnetic resonance imaging

<table>
<thead>
<tr>
<th>PIRADS</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive MRI*</td>
<td>30</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Cancer at TB (proportion)</td>
<td>11</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Gleason ≥ 7 PC at TB (proportion)</td>
<td>4 (13%)</td>
<td>1 (25%)</td>
<td>5 (100%)</td>
</tr>
<tr>
<td>Significant PC (proportion)</td>
<td>7 (23%)</td>
<td>3 (75%)</td>
<td>5 (100%)</td>
</tr>
</tbody>
</table>

MRI = magnetic resonance imaging; PC = prostate cancer; PIRADS = Prostate Imaging Reporting and Data System; TB = targeted biopsy.

* One man missing compared with Figure 1 and Table 1 due to a missing PIRADS score. He had an MRI classified as positive and underwent TB but the lesion was located in the left vesicula seminalis and hence, no PIRADS were determined. The biopsies turned out benign.

It is worth considering that men in this study had been invited to PSA-screenings at as many as nine times during 19 yr. Repeated screening reduces cancer incidence [36] and advanced disease [37]. Yet, MRI proved to be of great value even with repeatedly screened men with a similar positive predictive value of MRI in biopsy-naïve and previously biopsied men [48% vs 50%]. This indicates that MRI may be valuable even in follow-up screenings. Also, the negative predictive value was very high (87–92%) and in concordance with previous studies [38].

As stated above, men with PSA < 3.0ng/ml and a negative MRI were assumed cancer free. Verification bias may occur if disease verification differs according to test results. In an attempt to test for this, we performed a separate sensitivity analysis, where five hypothetical cancers were simulated to be present among men with nonsuspectitious MRIs and PSA values between 1.8–2.99ng/ml (data not shown). The choice of picking five cancers was based on findings from the Prostate Cancer Prevention Trial, which demonstrated a PC-prevalence of 19% (285/1480) in men with PSA 1.1–3.0ng/ml [6]. This analysis revealed that the significant differences between the three strategies remained with unchanged specificity but at a reduced sensitivity.

Another study limitation is that we lack information regarding interobserver variability among MRI readers. Another potential limitation is that fusion technology was not used to target biopsies (required equipment unavailable). In the large-scaled trial, comparisons between fusion and cognitive biopsies will be performed.

In summary, despite a heavily prescreened population, we found MRI to be a useful tool in detecting more significant PC compared with standard PSA-screening. Whether the extra cost associated with MRI outbalances the burden of unnecessary biopsies and overdiagnosis needs to be assessed in larger prospective studies, but this pilot study indicates a plausible way out of the dilemma in PC screening.

### 5. Conclusion

A new screening strategy for PC involving imaging with MRI appears to be highly accurate in detecting significant cancer and minimising unnecessary biopsies. If verified in the full-sized trial, these pilot results may contribute to a paradigm shift in the approach to early detection of PC.

**Author contributions:** Anna Grenabo Bergdahl had 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:** Hugosson, Geterud, Hellström, Grenabo Bergdahl, Khatami, Damber, Frånland.

**Acquisition of data:** Grenabo Bergdahl, Hugosson, Geterud, Socratous.

**Analysis and interpretation of data:** Grenabo Bergdahl, Wilderång, Hugosson, Carlsson.

**Drafting of the manuscript:** Grenabo Bergdahl, Hugosson.

**Critical revision of the manuscript for important intellectual content:** Aus, Stranne, Carlsson, Wilderång, Hugosson.

**Statistical analysis:** Grenabo Bergdahl, Wilderång, Hugosson.

**Obtaining funding:** Frånland, Khatami, Hugosson.

**Administrative, technical, or material support:** Frånland, Geterud, Hellström, Khatami, Damber.

**Supervision:** Hugosson, Aus.

**Other:** None.

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