SCANDINAVIAN JOURNAL OF UROLOGY
2021, VOL. 55, NO. 2, 116–124
https://doi.org/10.1080/21681805.2021.1881612

ARTICLE

OPEN ACCESS Check for updates

The GÖTEBORG prostate cancer screening 2 trial: a prospective, randomised, population-based prostate cancer screening trial with prostate-specific antigen testing followed by magnetic resonance imaging of the prostate

Kimia Kohestani[a,b], Marianne Månsson[a], Rebecka Arnsrud Godtman[a,b], Johan Stranne[a,b], Jonas Wallström[c,d], Sigrid Carlsson[a,e], Mikael Hellström[c,d] and Jonas Hugosson[a,b]

[a]Department of Urology, Institute of Clinical Sciences, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden; [b]Department of Urology, Region Västra Götaland, Sahlgrenska University Hospital, Gothenburg, Sweden; [c]Department of Radiology, Institute of Clinical Sciences, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden; [d]Department of Radiology, Region Västra Götaland, Sahlgrenska University Hospital, Gothenburg, Sweden; [e]Departments of Surgery (Urology Service) and Epidemiology and Biostatistics, Memorial Sloan Kettering Cancer Center, New York, NY, USA

ABSTRACT

Objective: To describe the study design of the GÖTEBORG prostate cancer screening (PC) 2 (Göteborg-2), a prospective, randomised, population-based trial of PC screening. This trial evaluates whether prostate-specific antigen (PSA) testing followed by 3 Tesla prostate magnetic resonance imaging (MRI) and targeted biopsy can reduce overdiagnosis, while maintaining the detection of clinically significant cancer, compared to PSA-screening and systematic biopsy.

Materials and methods: A random sample of men 50–60 years in the Göteborg area, Sweden, identified from the Total Population Register, were randomised to either a screening or control group (CG). Participants in the screening group (SG) were further randomised into one of three arms: (1) PSA-test; if PSA $\geq$ 3 ng/mL, then MRI and systematic biopsy, plus targeted biopsy to suspicious lesions as per Prostate Imaging – Reporting and Data System, version 2 (PI-RADSv2) 3–5; (2) PSA-test; if PSA $\geq$ 3 ng/mL, then MRI, and targeted biopsy only if PI-RADSv2 3–5; (3) identical to Arm 2, except lower PSA-cut-off $\geq$1.8 ng/mL. The primary outcome is the detection rate of clinically insignificant PC (defined as Gleason Score 3 + 3 [Grade Group 1]) comparing all men with PSA $\geq$ 3 ng/mL in Arm 1 *vs.* Arm 2 + 3.

Results: Randomisation and enrolment started in September 2015. Accrual has hitherto resulted in 38,770 men randomised to the SG. The participation rate is 50%. Invitation to the first screening round was completed in June 2020.

Conclusions: The Göteborg-2 trial will provide new knowledge about the performance of prostate MRI in a screening setting.

ARTICLE HISTORY
Received 2 November 2020
Revised 30 December 2020
Accepted 21 January 2021

KEYWORDS
Mass testing; screening; prostate cancer; prostate-specific antigen; MRI; study protocol

Introduction

Background and rationale

Curative treatment for localised prostate cancer (PC) is effective [1,2] and prostate-specific antigen (PSA) testing can enable the detection of PC at an early, curable stage [3–5]. The main problem with PSA-testing is overdiagnosis and the subsequent risk of overtreatment [6–8]. Due to the low specificity of the PSA-test many men are subjected to unnecessary biopsies with associated discomfort and risk of side-effects such as infections and bleeding [9,10]. The use of systematic biopsy technique, which was the standard clinical method until recently, together with the large number of slow-growing cancers in the prostate never causing harm, are the main mechanisms behind overdiagnosis [11,12].

Reduction of PC mortality by regular PSA-testing has been convincingly demonstrated [13–15]. However, the beneficial mortality reduction is not presently considered to outweigh the harms of screening. A refined screening strategy that maintains the PC mortality reduction while avoiding unnecessary biopsies and detection of clinically insignificant cancers, is much needed. In recent years, there has been a fundamental shift in the diagnostic work up of men with clinical suspicion of PC with magnetic resonance imaging (MRI) performed before prostate biopsy to guide, and sometimes even omit, biopsy [16]. MRI of the prostate is intended to discriminate insignificant cancers from harmful ones, and in this manner avoid unnecessary biopsies and overdiagnosis [17–19]. The findings of the PRECISION study, and several others, confirmed this and led to the recent paradigm shift in patients with clinical suspicion of cancer [20–23].

In a pilot study embedded within the last screening round of the Göteborg-1 trial, we evaluated prebiopsy MRI in a screening setting with promising results; MRI-targeted biopsy

CONTACT Jonas Hugosson jonas@urol.se Department of Urology, Institute for Clinical Sciences, Sahlgrenska Academy, University of Gothenburg, Bruna Stråket 11B, Gothenburg 413 45, Sweden

detected almost as many clinically significant cancers as the strategy with systematic biopsy, while reducing the detection rate of insignificant cancers [24]. However, the role of MRI as a screening tool has not yet been documented in large-scale, randomised screening trials. To bring clarity to this matter, we launched the "Göteborg-2 trial" in 2015, as a prospective, randomised, population-based trial of PC screening with PSA testing followed by prostate MRI. Herein, we describe the study design, procedures and participation rate of the trial.

Methods

Trial design

The GÖTEBORG prostate cancer screening 2 (Göteborg-2) trial is a single-centre study administered from the departments of Urology and Radiology, Institute of Clinical Sciences, Sahlgrenska Academy, University of Gothenburg. It is designed as a 2-step, 3-arm randomised screening study aiming to include at least 54,000 men and to compare different screening algorithms.

The study protocol is registered as International Standard Randomised Controlled Trial ISRCTN94604465. The trial website, with study protocol and amendments, is available at http://g2screening.se/

Objectives

Primary objective

The primary objective of the trial is to evaluate whether changing the screening algorithm in men with PSA $\geq$3 ng/mL from systematic biopsy to pre-biopsy MRI and MRI-targeted biopsy can reduce the risk of detecting clinically insignificant cancers.

Secondary objectives

1. To evaluate whether screening with pre-biopsy MRI and only MRI-targeted biopsy in men with PSA $\geq$ 3 ng/mL can maintain the detection rate of clinically significant cancer compared to systematic biopsy.
2. To evaluate whether detection of clinically significant PC can be improved in screening with pre-biopsy MRI and only MRI-targeted biopsy if the PSA-cut off is lowered from 3 to 1.8 ng/mL.
3. To evaluate whether bi-parametric MRI is non-inferior to multiparametric MRI in the detection of PC in a screening setting.
4. To evaluate whether screening with PSA and MRI can reduce PC mortality compared to no screening or opportunistic screening (comparing the screening group [SG] *vs.* the control group [CG]).

All outcome definitions are defined in Table 1. The primary definition of clinically significant PC is Gleason Score $\geq 3+4$ (also known as Grade Group 2) on biopsy but will also be analysed with other definitions provided in Table 2 [25].

Enrolment, randomisation and allocation concealment

The participants are randomised and enrolled in two steps. First, a random sample is identified from the Total Population Register of men aged 50–60 years in the city of

Table 1. Primary and secondary outcomes in Göteborg-2 trial.

Outcome	Definition	Time of assessment
Primary	Proportions of clinically insignificant cancers[a] Arm 1 vs Arm 2 + 3[b].	After completion of SR 1.
Primary	Proportions of clinically insignificant cancers[a] Arm 1 *vs.* Arm 2.	After completion of each SR after SR 1 (every 2 years).
Secondary	Proportions of clinically significant cancers[a] Arm 1 *vs.* Arm 2 + 3[b].	After completion of SR 1, 2 (at 2 and 4 years) and 8 years after SR 1.
Secondary	Cancer detection rate[c] bpMRI vs mpMRI.	After completion of SR 1.
Secondary	Proportion of clinically significant cancers Arm 2 *vs.* Arm 3.	After completion of each SR with start after SR 2.
Secondary	Cancer-specific incidence and mortality SG *vs.* CG (intention to screen analysis).	12 years after randomisation (31 December 2027) and every third year after.

SR: screening round; SG: screening group; CG: control group; bpMRI: bi-parametric MRI; mpMRI: multiparametric MRI
[a]Clinically insignificant cancer is primarily defined as Gleason score 3 + 3 in prostate biopsy and clinically significant cancer as Gleason score >3 + 3.
[b]The number of insignificant and significant cancers are only related to the number of men with PSA $\geq$ 3 ng/mL. Thus, cancers diagnosed in Arm 3 in men with PSA 1.8–3 will not be included in the statistical analysis.
[c]Cancer detection rate is defined as the ratio between number of men who are diagnosed with PC at biopsy and the total number of men who underwent MRI.

Table 2. Definitions of clinically significant cancer.

	Clinically significant cancer	Clinically insignificant cancer
Primary definition	Gleason score $\geq$ 3 + 4	Gleason score = 3 + 3
Definition 2[a]		Gleason score = 3 + 3, Clinical stage T1C, PSA-density < 0.15, $\leq$ 2 positive sectors and unilateral cancer
Definition 3[b]	Gleason score $\geq$ 4 + 3, or cancer core $\geq$ 6 mm	
Definition 4[b]	Gleason score $\geq$ 3 + 4, or cancer core $\geq$ 4 mm	

[a]In definition 2, the modified Epstein criteria is used. In order to not overestimate cancer extent in men who underwent targeted biopsies, the number of positive cores is translated into positive sectors.
[b]Definitions 3 and 4 are adapted from the PROMIS trial [17]. For cancer core length in targeted biopsies a mean value is calculated from the three to four cores of targeted biopsies.

Gothenburg, Sweden and six surrounding municipalities [26]. To ensure full allocation concealment, a secure, password-protected computer-based algorithm performed by an external person without the study investigators' involvement is used. The sample is updated from the Total Population Register every three months. Men in this sample are randomised to either the screening group (SG) or the control group (CG). When invitation started in September 2015, the allocation ratio was 1:1. Since January 2017, due to an observed lower than anticipated participation rate, the allocation was changed to 2:1 in order to reach a sufficient sample size in the SG to evaluate the primary objective at four years. In order to achieve comparable groups, half of the CG before this date was randomly selected based on age group and geographical region for the main analysis.

In the second step, men randomised to the SG and fulfilling the eligibility criteria (Table 3) are invited for PSA-testing. Men accepting participation are further allocated to one of the three screening-arms.

Screening intervention

Men in the SG are subjected to different screening strategies depending on arm allocation (Figure 1):

1. Arm 1 (reference arm): PSA $\geq$ 3 ng/mL leads to further evaluation with prostate MRI followed by systematic biopsy – regardless of MRI result. Targeted biopsies are added in case of suspicious lesions (PI-RADS 3–5) on MRI.
2. Arm 2: PSA $\geq$ 3 ng/mL leads to further evaluation with prostate MRI, followed by targeted biopsy in men with suspicious lesions (PI-RADS 3-5) on MRI.
3. Arm 3: is identical to arm 2 except that the PSA-cut off for biopsy is lower, 1.8 ng/mL.

Irrespective of MRI results, due to high risk of lethal cancer and in order to harmonise with the Swedish national guidelines, men in Arms 2 and 3 with PSA $\geq$ 10 ng/mL are recommended systematic biopsy. Participants with PSA-levels below the cut-offs for further evaluation according to arm

Table 3. Eligibility criteria.

Inclusion criteria	Exclusion criteria
• Alive on randomisation date • A registered address in the county of Gothenburg or any of six specified surrounding municipalities in Sweden • Age 50–60 years	• Previous diagnosis of prostate cancer • Emigration during the period between randomisation and update of the Total Population Register, to which the study participants' unique personal identification numbers are linked. • Death during the period between randomisation and update of the Total Population Register, to which the study participants' unique personal identification numbers are linked.

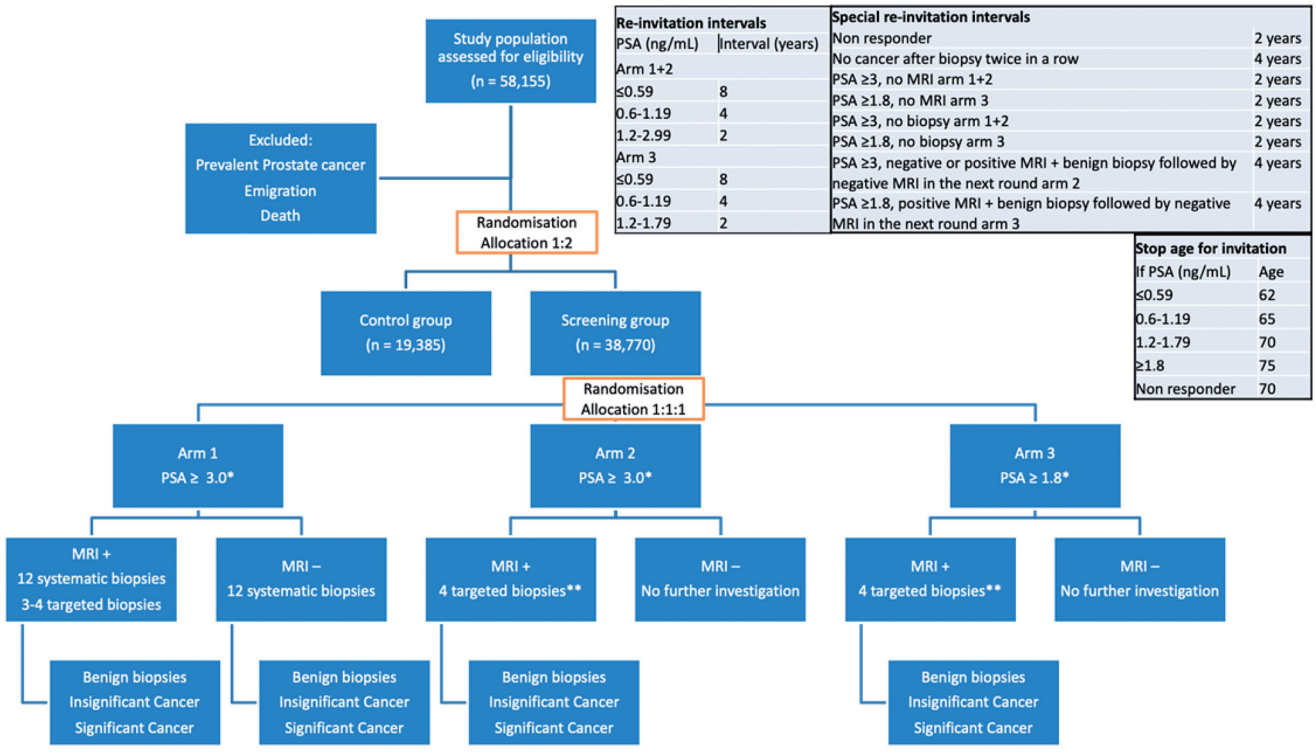

Figure 1. Study Schema of the Göteborg-2 trial. Figure 1 shows the study layout of the Göteborg-2 trial. MRI interpretation is performed according to *Prostate Imaging-Reporting and Data System (PI-RADS)*, v.2.1. MRI +: positive MRI defined as PI-RADS 3, 4 or 5. MRI−: negative MRI defined as PI-RADS 1 or 2. *All men with PSA $\geq$ 10.0 ng/mL are recommended 12-core systematic TRUS biopsy plus additional targeted biopsy if positive MRI. **All men with an MRI showing PI-RADS 5 are recommended 12-core systematic TRUS biopsy.

allocation are re-invited at pre-specified re-screening intervals given in Figure 1. Similarly, all participants with PSA-levels above the cut-offs who have benign biopsies and participants in Arms 2 and 3 without suspicious MRI-lesions are re-invited. Termination of screening is determined by participant age in combination with the last PSA-value as described in Figure 1.

Equipment and infrastructure

Blood sampling

Blood sampling for PSA and pre-MRI serum creatinine is offered at 13 health care facilities in the region (one hospital and 12 primary care facilities). Approximately 5 mL of blood is sampled in heparinised tubes and stored in a refrigerator until transported to the laboratory. All blood samples are analysed by a central laboratory (UniLabs Sweden Ltd, Skövde, Sweden) using Advia Centaur XP and XPT (Siemens Healthcare Diagnostics Inc. US and Germany). PSA is analysed within 24 h from blood draw unless the blood tests are obtained before a weekend (72 h).

Imaging – protocol and review

MR imaging is performed at the Department of Radiology, Sahlgrenska University Hospital using a 3-Tesla scanner (Philips Medical System) with a pelvic phased-array coil. Preparation includes 4 h of fasting and a micro-enema 2 h prior to imaging. Compliant to the PI-RADSv2 (Prostate Imaging – Reporting and Data System) guidelines [19], multiparametric MRI is performed with three sequences; multiplanar fast spin echo T2-weighted imaging, axial diffusion-weighted imaging with b-values of 0, 100, 1000 and 1500 s/mm^2, all but b-value of 0 used for calculation of the apparent diffusion coefficient-map, and axial dynamic contrast-enhanced T1-weighted imaging as the final sequence, with the administration of gadolinium-based contrast medium.

All images are read by two out of three radiologists (all with >5 years of prostate MRI experience) in consensus and blinded to trial arm, PSA-level and clinical data. MRI findings are classified according to the most current PI-RADS version (PI-RADSv2.0 from study start until 1 June 2019 when the updated protocol PIRADSv.2.1 was introduced). A positive MRI is defined as PI-RADS 3–5. Each lesion is given a localisation according to a 24-sector template, based on the Swedish National PC Guidelines [27]. From April 2019, the protocol for multiparametric MRI is only used in screening round 1. All men referred for MRI in subsequent screening rounds (round 2 and onwards) undergo bi-parametric MRI without the contrast medium sequence.

Urological examination and biopsy

Participants with an indication for prostate biopsy are scheduled for an examination by an experienced urologist with digital rectal examination (DRE) and transrectal ultrasound (TRUS) followed by TRUS guided biopsy of the prostate. The assessment of clinical tumour (T) stage and TRUS findings are performed blinded to trial arm, PSA-level and MRI-results. After unblinding of the MRI-results, men are subjected to prostate biopsy according to the protocol for their allocated screening arm (Figure 1). An amount of 750 mg ciprofloxacin is administered as a single dose before biopsy. Prolonged prophylaxis is given in men with increased risk of infection according to the Swedish National PC Guidelines [27]. Systematic biopsy with 12 cores is obtained from the peripheral zone of the prostate and their localisation described according to the previously mentioned national template. For men with suspicious lesions on MRI (PI-RADS 3–5), targeted biopsy is obtained with four cores directed towards the sector in which the centre of each MRI lesion is described; if systematic biopsy has already been directed to a sector, only three targeted cores are added. All men in Arms 2 and 3 with PC detected at targeted biopsy are rebiopsied with systematic biopsy in order to judge cancer extension in the prostate.

Central pathology review

All prostate biopsies are centrally reviewed by one experienced prostate pathologist at the department of Pathology, Sahlgrenska University Hospital. To validate the histopathology diagnoses, all cancers detected during the first screening round will be reviewed by two external specialised prostate pathologists.

Management of database and data collection

Data are prospectively and continuously recorded in a central database located at University of Gothenburg and will be kept for 30 years from study start. Extraction of data from the database is regulated in the protocol and logged. PSA-results and MRI results are digitally transferred to the database on a regular basis. Clinical variables at TRUS examination are entered directly by the urologist into the study database. Participant questionnaires are self-administered and collected electronically at baseline and at follow-up visits.

The management of data ensures the privacy of the subjects. Data will be analysed and reported only on group levels and no data will be linked to any individual.

Voluntariness and ethical considerations

The Regional Ethics Review Board at Gothenburg University approved the Göteborg-2 trial in January 2015, registration number 890-14.

All men randomised to the SG or CG receive by postal mail detailed information about the study, its design, benefits and risks, contact details and a reference link to the study website. The website also includes a link to the Swedish National Board of Health and Welfare's written information about PSA-testing and its pros and cons. Men in both groups are informed that participation is voluntary and can be terminated at any time by a deliberate action of the participant (opt out procedure). Written informed consent is

thus not requested from participants in the main study but is requested in some side studies.

Advisory board and processing of adverse events

An external advisory board recruited from national and international experts in the field has been established. Adverse events from MRI and TRUS biopsy are recorded continuously, including contrast allergy requiring medication and infections complications after biopsies, with or without hospitalisation.

Stopping rules

In the main, the study protocol follows clinical recommendations from the Swedish Board of Health and Welfare. One critical point has been identified concerning a potential delay of diagnosing serious cancer when omitting biopsy in men with a negative MRI (and a PSA $<$ 10) in Arms 2 and 3. Therefore, annual analysis of the incidence of interval cancers in these men is planned as well as studying the incidence of serious cancers detected at follow-up screens in men with elevated PSA and negative MRI in previous screening rounds. These data will be presented to the Advisory Board for recommendations. No other stopping rules are specified within the protocol.

Sample size calculation

We based the sample size calculation for the primary endpoint on a power of 80% and alpha 0.05, using a two-sided test, hypothesising that the reduction in insignificant PC with the MRI-targeted biopsy strategy would be 50% as compared to systematic biopsy. Based on previous studies and expert knowledge, we assumed that the proportion of men

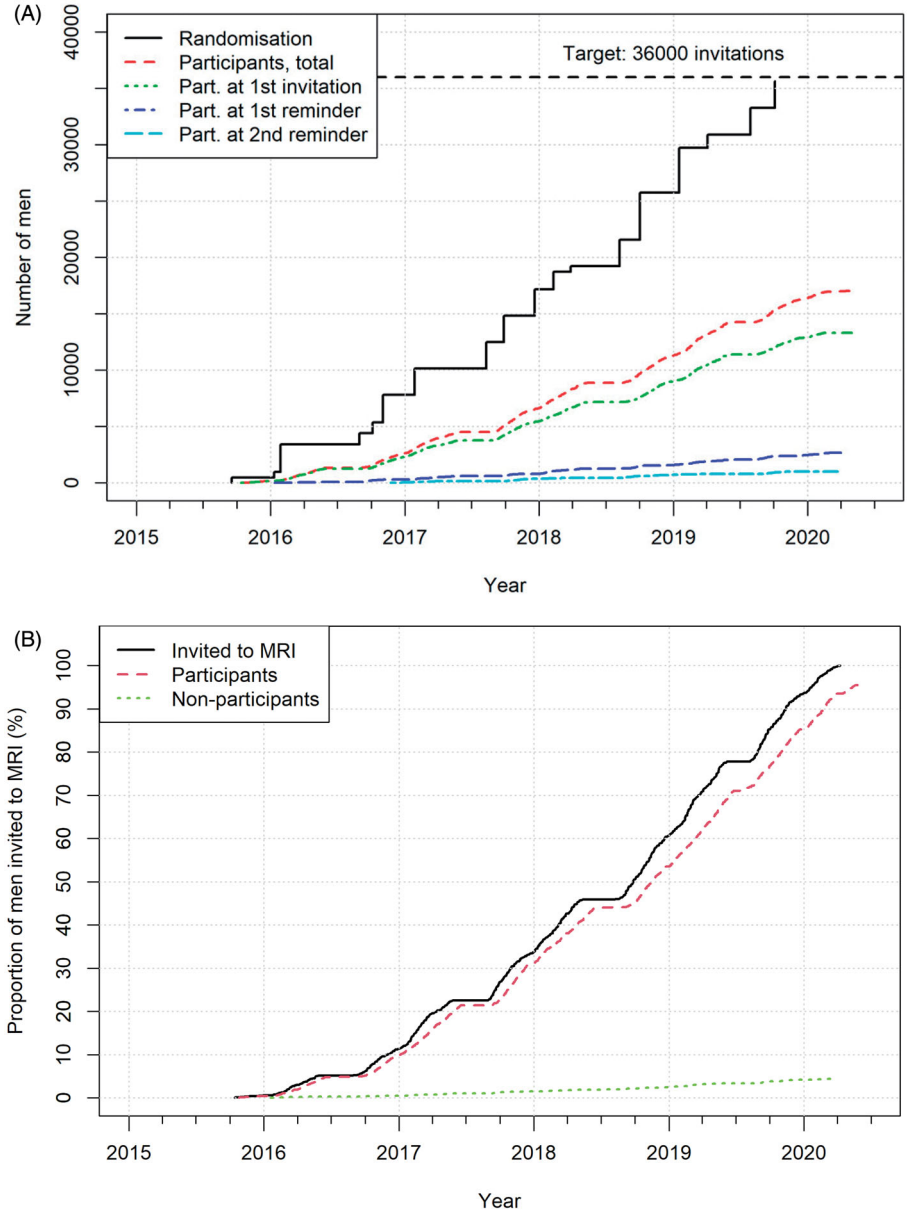

Figure 2. (A–C) Enrolment and participation rates. (A) Accrual rate, (B) Participation rate and further evaluation with prostate MRI. (C) Participation rate and further evaluation with TRUS biopsy.

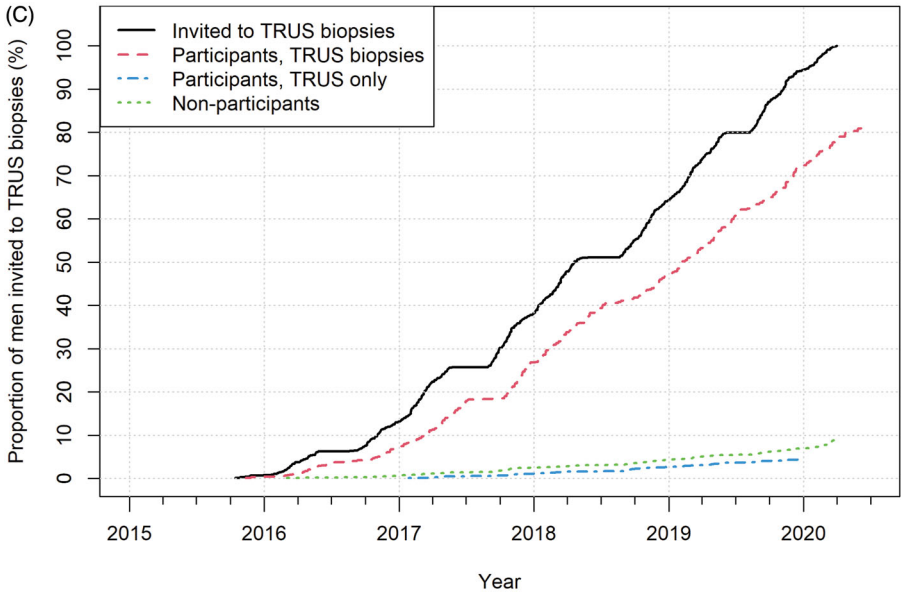

Figure 2. (Continued).

diagnosed with insignificant PC among men with PSA $\geq$ 3 in Arm 1 (reference arm) would be 9%. This gave a sample size of $N = 1164$ men with PSA $\geq$ 3 ng/mL. Furthermore, we hypothesised that 7% among men attending PSA-screening would have an elevated PSA and that the participation rate would be 50%, which lead to the sample size $N = 33{,}260$ altogether in the three screening-arms. Accounting for uncertainty in the hypothesised proportion of insignificant PCs and in the proportion of men with PSA $\geq$ 3 ng/mL among those screened, lead to the final sample size of $N = 36{,}000$ for the SG. With an allocation rate of 1:2 between the CG and SG, altogether, $N = 54{,}000$ men are needed to be included in the study.

Side-studies

A number of side-studies are planned within this trial, including the evaluation of: morbidity related to the screening algorithms, technical aspects of MRI, feasibility and logistics, costs and cost-effectiveness, patient-reported outcomes and quality-of-life, biomarkers (blood, urine and biopsy tissue is sampled and biobanked), equitable care and health care disparities. The hypotheses, objectives and statistical analysis plans of these sides-studies will be described in separate publications.

Results

The first participants were randomised and invited in September 2015. The complete cohort has been randomised in spring 2020 reaching beyond the target with 38,770 men invited to the SG and 23,347 men to the CG (of whom 19,385 men will be analysed). The opt-out rates up to September 2020 are 1.0% and 2.2% in the SG and CG, respectively.

The accrual rate for men randomised up-until 31 December 2019 is shown in Figure 2(A). The participation rate is 50% and the majority of participants, 75%, chose to attend when receiving the first invitation, and a minor number following invitation reminders.

The vast majority of men attended further evaluation according to the study protocol, when invited to MRI (94%) and TRUS biopsies (85%), as shown in Figure 2(B,C). Reasons for not performing MRI and proportions of MRIs of non-diagnostic quality are shown in Figure 3(A). Reasons for not performing TRUS biopsies are shown in Figure 3(B). Of the participants who did not undergo MRI, 48% were clinically assessed and 70% of these underwent biopsies.

The age distribution at randomisation in the SG is shown in Figure 4. As seen, the number of randomised men is higher in the youngest and oldest age groups.

Discussion

The aim of the Göteborg-2 trial is to evaluate whether PSA-screening followed by prostate MRI, compared to PSA-screening without MRI, can reduce overdiagnosis and maintain (or increase) the detection rate of clinically significant PC. Since the definition of clinically significant cancer still is under debate with no golden standard, we use different pre-specified definitions of significant PC for the analyses, Table 3 [28].

The Göteborg-2 trial uses the Zelen double consent design with randomisation before consent [29]. Further no active consent was necessary and only men opting out were excluded from the study. This approach can be viewed as controversial by some but allows evaluating the effectiveness of the screening trial (secondary outcome i.e. PC mortality) due to the very low rate of opting out (1.0% in the SG and 2.2% in the CG) as compared to an efficacy design with upfront consent where 50% acceptance rate is common [30].

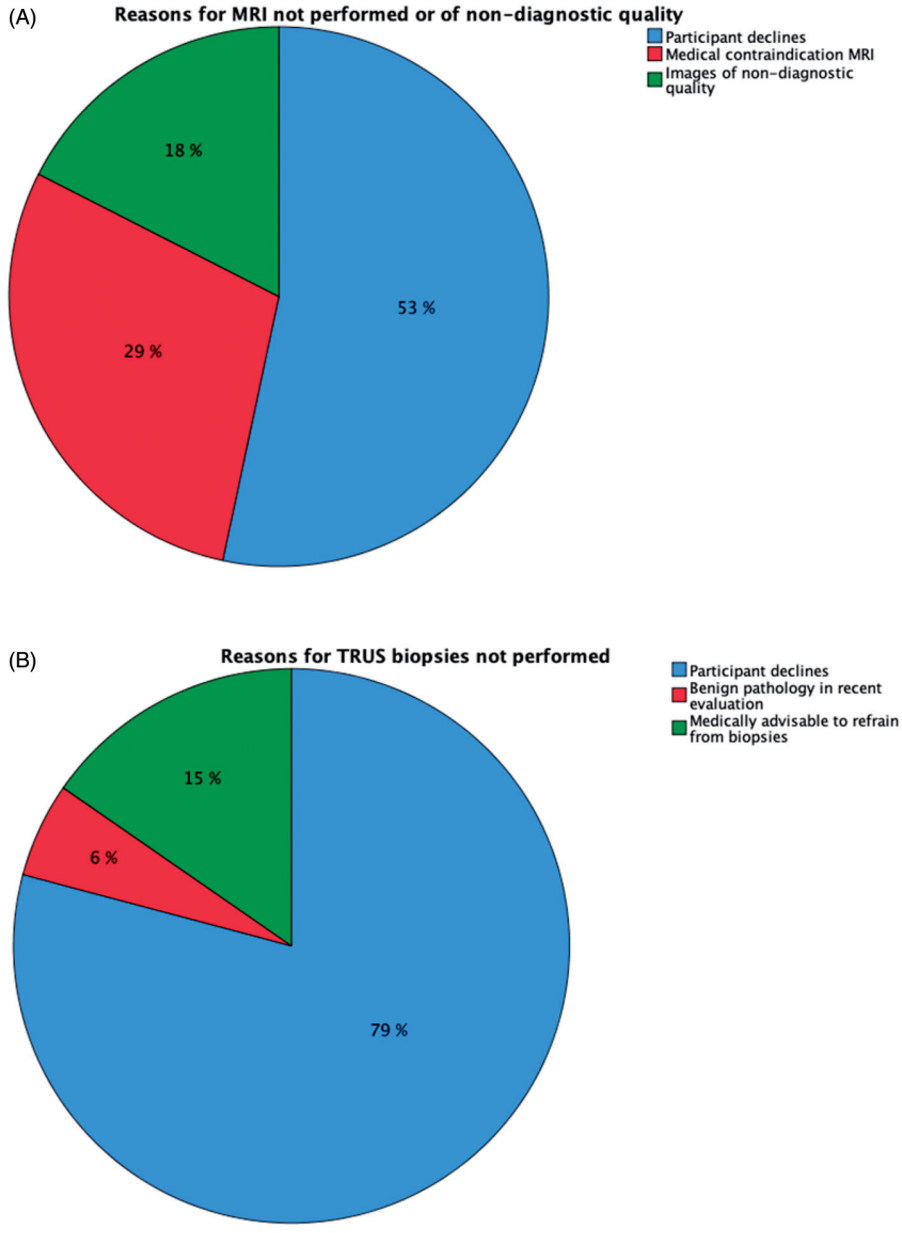

Figure 3. (A) Reasons for MRI not performed or MRI of non-diagnostic quality.Of the planned MR exams, 6% were not performed (due to participant declining or having a medical contraindication) or of non-diagnostic quality (mainly due to hip-prostheses or other osteosynthesis material distorting the diffusion-weighted sequence but also due to claustrophobia rendering incomplete examinations). (B) Reasons for TRUS biopsies not performed. Of the planned TRUS biopsies, 15% were not performed.

It is well-known that opportunistic PSA-testing occurs frequently in Sweden, as in many other countries, and approximately 25% of 50-year olds and 50% of 60-year olds in Gothenburg and the surrounding region has measured their PSA [31]. However, since we sought to primarily evaluate different screening algorithms rather than screening *vs.* no screening, we do not anticipate contamination bias to be a major problem in the primary outcome of this study.

Analysing the secondary outcome concerning PC mortality in the SG *vs.* the CG, contamination is inevitable and cannot be disregarded. Although opportunistic PSA-testing is less effective than organised PSA-screening regarding PC mortality [32], contamination might dilute the difference between the groups and slightly reduce the power of the study to detect a difference in PC mortality between them. However, this will be addressed in analyses adjusting for contamination as well as by comparing the SG to historical controls.

The uneven age distribution at randomisation is explained by the procedure of randomisation and enrolment. In order to include 60-year olds before they are no longer eligible, they were prioritized for randomisation from the population-based sample. Furthermore, the sample is updated from the Total Population Register every 3 months; it will continuously be refilled with new 50-year olds explaining their relatively high frequency.

Since the start in September 2015, the accrual has progressed well. Besides some adjustments to the protocol concerning safety matters and a minor delay due to the Covid-19 pandemic, there are no issues concerning feasibility.

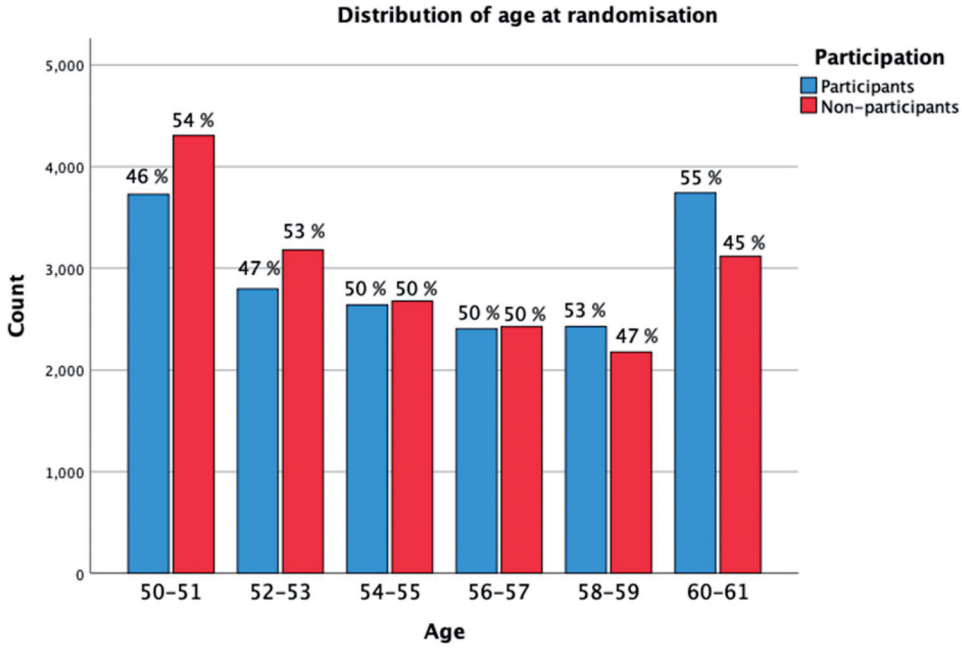

Figure 4. Age distribution at randomisation. Due to time delay between the identification of the first random sample from the Total Population Register and the randomisation to control or screening group, some men turn 61. They make 1% of the randomised men up-until 31 December 2019.

In comparison with similar research efforts around the world, there are a few other ongoing trials investigating screening with PSA and MRI (ProScreen, Finland, STHLM3MR2, Sweden, PROBASE, Germany). The results of the Göteborg-2 trial will provide new valuable information on novel approaches to screening and early detection of PC to help customise future screening programs for PC. If PSA-testing followed by MRI and targeted biopsy can shift the ratio of benefits-to-harms of PC screening, there will be a paradigm shift opening up for population-based screening for PC.

Acknowledgements

A large-scale trial like this would not be possible without the never-ending blood sampling by the collaborating health care facilities and the excellent work of the personnel at the trial secretariat and the study nurses at the Radiology and Urology departments at the Sahlgrenska University Hospital in Gothenburg, Sweden, to whom the authors are very grateful.

Disclosure statement

None of the authors has any conflict of interest to declare. The authors alone are responsible for the content and writing of the article.

Funding

The Göteborg 2-trial is supported by grants from Karin and Christer Johansson's Foundation for Research and Education, the Swedish Cancer Society (contract number CAN 2016/492 and CAN 2017/620), the Swedish state under the agreement between the Swedish government and the county councils, the ALF-agreement (ALFGBG671851, ALFGBG724401 and ALFGBG774531), Regional Cancer Center West (Sweden), Swedish Research Council (Contract number 2016/01973). Sigrid Carlsson's work was supported in part by funding from the National Institutes of Health/National Cancer Institute (P30-CA008748). Part of Kimia Kohestanis work on this paper was supported by Anna-Lisa and Bror Björnsson's Foundation.

ORCID

Kimia Kohestani http://orcid.org/0000-0003-0244-5508
Marianne Månsson http://orcid.org/0000-0002-1460-4062
Rebecka Arnsrud Godtman http://orcid.org/0000-0003-2061-6550
Johan Stranne http://orcid.org/0000-0002-4295-6524
Jonas Wallström http://orcid.org/0000-0002-4453-6718
Sigrid Carlsson http://orcid.org/0000-0003-3553-5710
Mikael Hellström http://orcid.org/0000-0003-4031-332X

References

[1] Bill-Axelson A, Holmberg L, Garmo H, et al. Radical prostatectomy or watchful waiting in early prostate cancer. N Engl J Med. 2014; 370(10):932–942.
[2] Kupelian PA, Potters L, Khuntia D, et al. Radical prostatectomy, external beam radiotherapy <72 Gy, external beam radiotherapy > or =72 Gy, permanent seed implantation, or combined seeds/external beam radiotherapy for stage T1-T2 prostate cancer. Int J Radiat Oncol Biol Phys. 2004;58(1):25–33.
[3] Stamey TA, Yang N, Hay AR, et al. Prostate-specific antigen as a serum marker for adenocarcinoma of the prostate. N Engl J Med. 1987;317(15):909–916.
[4] Catalona WJ, Smith DS, Ratliff TL, et al. Measurement of prostate-specific antigen in serum as a screening test for prostate cancer. N Engl J Med. 1991;324(17):1156–1161.
[5] Stephenson AJ, Kattan MW, Eastham JA, et al. Prostate cancer-specific mortality after radical prostatectomy for patients treated in the prostate-specific antigen era. J Clin Oncol. 2009;27(26): 4300–4305.
[6] Draisma G, Boer R, Otto SJ, et al. Lead times and overdetection due to prostate-specific antigen screening: estimates from the European Randomized Study of Screening for Prostate Cancer. J Natl Cancer Inst. 2003;95(12):868–878.

[7] Heijnsdijk EA, der Kinderen A, Wever EM, et al. Overdetection, overtreatment and costs in prostate-specific antigen screening for prostate cancer. Br J Cancer. 2009;101(11):1833–1838.
[8] Loeb S, Bjurlin MA, Nicholson J, et al. Overdiagnosis and overtreatment of prostate cancer. Eur Urol. 2014;65(6):1046–1055.
[9] Loeb S, Vellekoop A, Ahmed HU, et al. Systematic review of complications of prostate biopsy. Eur Urol. 2013;64:876–892.
[10] Stattin P, Vickers AJ, Sjoberg DD, et al. Improving the specificity of screening for lethal prostate cancer using prostate-specific antigen and a panel of kallikrein markers: a nested case-control study. Eur Urol. 2015;68(2):207–213.
[11] Soos G, Tsakiris I, Szanto J, et al. The prevalence of prostate carcinoma and its precursor in Hungary: an autopsy study. Eur Urol. 2005;48(5):739–744.
[12] Zlotta AR, Egawa S, Pushkar D, et al. Prevalence of prostate cancer on autopsy: cross-sectional study on unscreened Caucasian and Asian men. J Natl Cancer Inst. 2013;105(14):1050–1058.
[13] Schroder FH, Hugosson J, Roobol MJ, et al. Screening and prostate cancer mortality: results of the European Randomised Study of Screening for Prostate Cancer (ERSPC) at 13 years of follow-up. Lancet. 2014;384:2027–2035.
[14] Hugosson J, Godtman RA, Carlsson SV, et al. Eighteen-year follow-up of the Göteborg Randomized Population-based Prostate Cancer Screening Trial: effect of sociodemographic variables on participation, prostate cancer incidence and mortality . Scand J Urol. 2018;52(1):27–37.
[15] Tsodikov A, Gulati R, Heijnsdijk EAM, et al. Reconciling the effects of screening on prostate cancer mortality in the ERSPC and PLCO trials. Ann Intern Med. 2017;167(7):449–455.
[16] Mottet N, Briers E, Cornford P, et al. EAU - EANM - ESTRO - ESUR - SIOG guidelines on prostate cancer: EAU guidelines office, Arnhem, The Netherlands: 2019. [28 June 2019]. Available from: https://uroweb.org/guideline/prostate-cancer/
[17] Ahmed HU, El-Shater Bosaily A, Brown LC, et al. Diagnostic accuracy of multi-parametric MRI and TRUS biopsy in prostate cancer (PROMIS): a paired validating confirmatory study. Lancet. 2017;389(10071):815–822.
[18] Rouviere O, Puech P, Renard-Penna R, et al. Use of prostate systematic and targeted biopsy on the basis of multiparametric MRI in biopsy-naive patients (MRI-FIRST): a prospective, multicentre, paired diagnostic study. Lancet Oncol. 2019;20(1):100–109.
[19] Turkbey B, Rosenkrantz AB, Haider MA, et al. Prostate imaging reporting and data system version 2.1: 2019 update of prostate imaging reporting and data system version 2. Eur Urol. 2019;76(3):340–351.
[20] Schoots IG, Padhani AR, Rouviere O, et al. Analysis of magnetic resonance imaging-directed biopsy strategies for changing the paradigm of prostate cancer diagnosis. Eur Urol Oncol. 2020;3(1):32–41.
[21] Sathianathen NJ, Omer A, Harriss E, et al. Negative predictive value of multiparametric magnetic resonance imaging in the detection of clinically significant prostate cancer in the prostate imaging reporting and data system era: a systematic review and meta-analysis. Eur Urol. 2020;78(3):402–414.
[22] Drost FH, Osses D, Nieboer D, et al. Prostate magnetic resonance imaging, with or without magnetic resonance imaging-targeted biopsy, and systematic biopsy for detecting prostate cancer: a Cochrane systematic review and meta-analysis. Eur Urol. 2020;77(1):78–94.
[23] Kasivisvanathan V, Rannikko AS, Borghi M, et al. MRI-targeted or standard biopsy for prostate-cancer diagnosis. N Engl J Med. 2018;378(19):1767–1777.
[24] Grenabo Bergdahl A, Wilderang U, Aus G, et al. Role of magnetic resonance imaging in prostate cancer screening: a pilot study within the Goteborg randomised screening trial. Eur Urol. 2016;70(4):566–573.
[25] Epstein JI, Egevad L, Amin MB, et al. The 2014 international society of urological pathology (ISUP) consensus conference on Gleason grading of prostatic carcinoma: definition of grading patterns and proposal for a new grading system. Am J Surg Pathol. 2016;40(2):244–252.
[26] Scb SS. Registret över totalbefolkningen (RTB), total population register 2020. [cited 2020 12 Oct]. Available from: https://www.scb.se/vara-tjanster/bestalla-mikrodata/vilka-mikrodata-finns/individregister/registret-over-totalbefolkningen-rtb/
[27] Samverkan VfpRci. Nationellt vårdprogram prostatacancer. 2020, March 3 [2020-06-08]. Available from: https://kunskapsbanken.cancercentrum.se/diagnoser/prostatacancer/vardprogram/
[28] Van der Kwast TH, Roobol MJ. Defining the threshold for significant versus insignificant prostate cancer. Nat Rev Urol. 2013;10(8):473–482.
[29] Zelen M. A new design for randomized clinical trials. N Engl J Med. 1979;300(22):1242–1245.
[30] Roobol MJ, Kranse R, Bangma CH, et al. Screening for prostate cancer: results of the rotterdam section of the European randomized study of screening for prostate cancer. Eur Urol. 2013;64(4):530–539.
[31] Regional cancercentrum väst. Förstudie: organiserad prostatacancertestning i VGR 2019 [December 23, 2020]. Available from: https://cancercentrum.se/globalassets/vara-uppdrag/prevention-tidig-upptackt/prostatacancertestning/vgr-forstudie-organiserad-prostatacancertestning.pdf
[32] Arnsrud Godtman R, Holmberg E, Lilja H, et al. Opportunistic testing versus organized prostate-specific antigen screening: outcome after 18 years in the Göteborg randomized population-based prostate cancer screening trial . Eur Urol. 2015;68(3):354–360.