Screening av prostatacancer, bilddiagnostikens roll

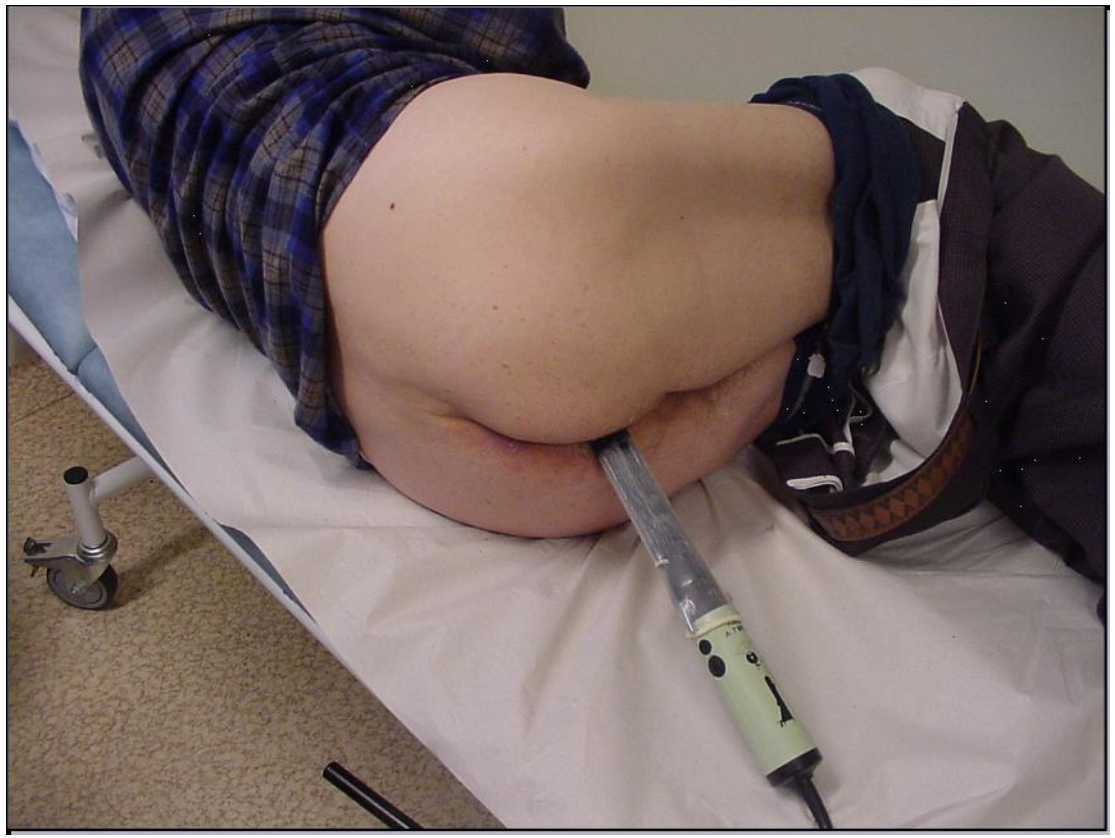
Jonas Hugosson

Professor i Urologi, Sahlgrenskaakademin, Göteborgs Universitet

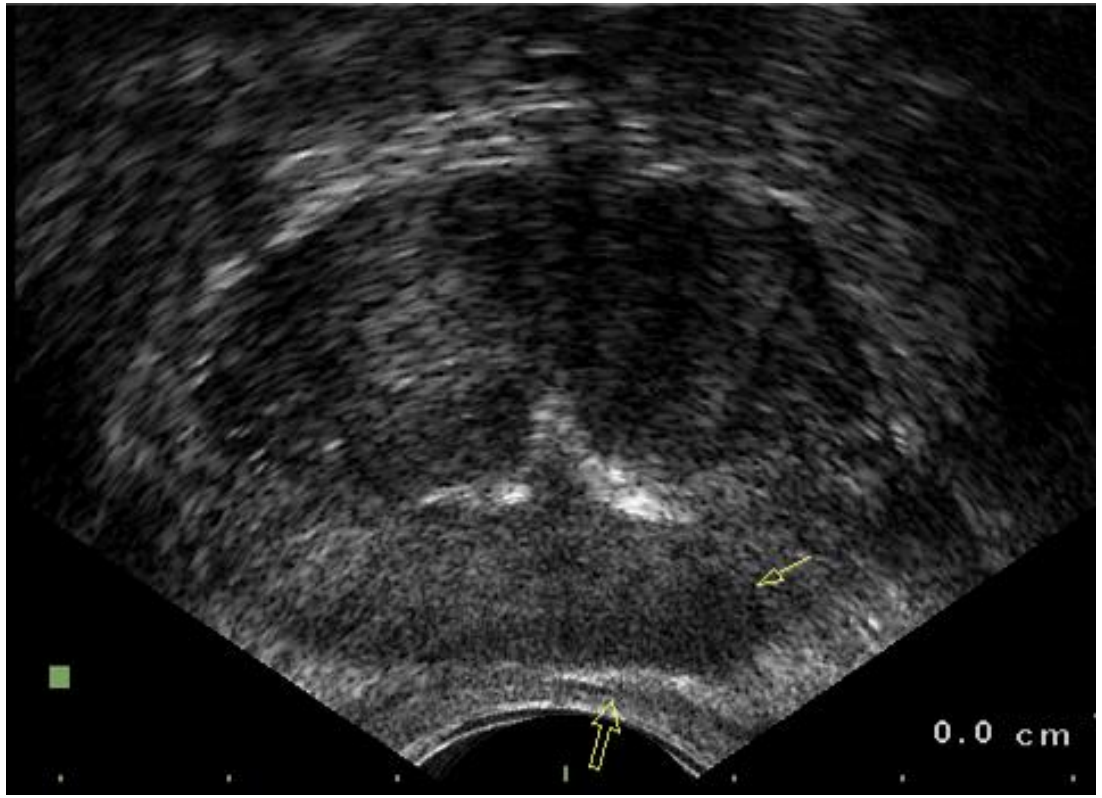
Överläkare, Verksamhet Urologi, Sahlgrenska Universitetssjukhuset

Det blir svårare och svårare…

- På 80-talet diagnosticerade vi prostatacancer (PC) hos patienter med hjälp av rektalpalpation och finnålscytologi. Behandlingen var kastration vid symptom
- På 90-talet kom prostata-specifikt antigen (PSA) som fullständigt förändrade patientpanoramat. Samtidigt kom transrektalt ultraljud och mellannålsbiopsi. Kurativ behandling infördes
- Screening blev aktuell och PSA som screening verktyg utvärderas i flera stora randomiserade studier.
- Runt 2010 kom MR som nästa revolution i prostatacancer diagnostiken
- Introduktion av ny bilddiagnostik (fr a PET) kommer att med stor sannolikhet ytterligare förändra hur vi kommer att diagnosticera och behandla PC



Transrektalt ultraljud (TRUL) har sedan 30 år varit urologens förlängda finger



Sensitiviteten att hitta cancer med TRUL är lite bättre än enbart fingret, cirka 50 %, men specificiteten är mycket låg

TRUL är ett utmärkt instrument för att guida biopsinålar till de områden man vill biopsera. Eftersom TRUL har låg specificitet och ett förhöjt PSA inte ger någon vägledning var en eventuell tumör är belägen utvecklades tekniken med systematiska biopsier.

Systematiska biopsier innebär att man tar 10-16 spridda nålar från prostata för att täcka hela prostatans dorsala del (perifera zonen)

INCIDENS OCH DÖDLIGHET I PROSTATACANCER JÄMFÖRT MED BRÖSTCANCER

	Prostatacancer antal insjuknade	Prostatacancer antal döda	Bröstcancer antal insjuknade	Bröstcancer antal döda
1970	2841		3392	
1997	5940	2448	5832	1494
2003		2625		
2004				1572
2019	11017	2223	10939	1356
2019 < 60 år		24		257
2019 < 50 år		2		97

Experience of PSA-based screening, ERSPC (707 publications)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Screening and Prostate-Cancer Mortality in a Randomized European Study

Fritz H. Schröder, M.D., Jonas Hugosson, M.D., Monique J. Roobol, Ph.D., Teuvo L.J. Tammela, M.D., Stefano Ciatto, M.D., Vera Nelen, M.D., Maciej Kwiatkowski, M.D., Marcos Lujan, M.D., Hans Lilja, M.D., Marco Zappa, Ph.D., Louis J. Denis, M.D., Franz Recker, M.D., Antonio Berenguer, M.D., Liisa Määttänen, Ph.D., Chris H. Bangma, M.D., Gunnar Aus, M.D., Arnauld Villers, M.D., Xavier Rebillard, M.D., Theodorus van der Kwast, M.D., Bert G. Blijenberg, Ph.D., Sue M. Moss, Ph.D., Harry J. de Koning, M.D., and Anssi Auvinen, M.D., for the ERSPC Investigators*

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 15, 2012 VOL. 366 NO. 11

Prostate-Cancer Mortality at 11 Years of Follow-up

Fritz H. Schröder, M.D., Jonas Hugosson, M.D., Monique J. Roobol, Ph.D., Teuvo L.J. Tammela, M.D., Stefano Ciatto, M.D., Vera Nelen, M.D., Maciej Kwiatkowski, M.D., Marcos Lujan, M.D., Hans Lilja, M.D., Marco Zappa, Ph.D., Louis J. Denis, M.D., Franz Recker, M.D., Alvaro Páez, M.D., Liisa Määttänen, Ph.D., Chris H. Bangma, M.D., Gunnar Aus, M.D., Sigrid Carlsson, M.D., Arnauld Villers, M.D., Xavier Rebillard, M.D.,

Screening and prostate cancer mortality: results of the European Randomised Study of Screening for Prostate Cancer (ERSPC) at 13 years of follow-up

Fritz H Schröder, Jonas Hugosson, Monique J Roobol, Teuvo L J Tammela, Marco Zappa, Vera Nelen, Maciej Kwiatkowski, Marcos Lujan, Liisa Määttänen, Hans Lilja, Louis J Denis, Franz Recker, Alvaro Paez, Chris H Bangma, Sigrid Carlsson, Donella Puliti, Arnauld Villers, Xavier Rebillard, Matti Hakama, Ulf-Hakan Stenman, Paula Kujala, Kimmo Taari, Gunnar Aus, Andreas Huber, Theo H van der Kwast, Ron H N van Schaik, Harry J de Koning, Sue M Moss, Anssi Auvinen, for the ERSPC Investigators*

eau European Association of Urology

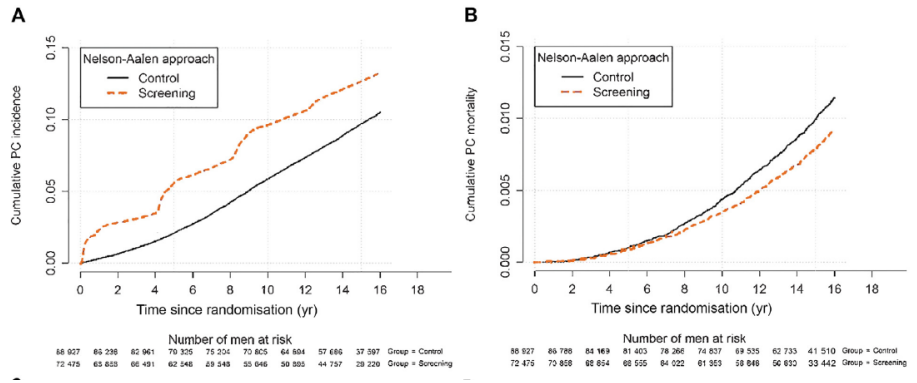
Platinum Priority – Prostate Cancer – Editor's Choice

Editorial by Gunnar Steineck, Olof Akre and Anna Bill-Axelson on pp. 52–53 of this issue

A 16-yr Follow-up of the European Randomized study of Screening for Prostate Cancer

Jonas Hugosson[a,], Monique J. Roobol[b], Marianne Månsson[a], Teuvo L.J. Tammela[c], Marco Zappa[d], Vera Nelen[e], Maciej Kwiatkowski[f,g], Marcos Lujan[h], Sigrid V. Carlsson[a,i], Kirsi M. Talala[j], Hans Lilja[k,l,m,n,o], Louis J. Denis[p], Franz Recker[f], Alvaro Paez[q], Donella Puliti[d], Arnauld Villers[r], Xavier Rebillard[s], Tuomas P. Kilpeläinen[t], Ulf H. Stenman[u], Rebecka Arnsrud Godtman[a], Karin Stinesen Kollberg[a], Sue M. Moss[v], Paula Kujala[u], Kimmo Taari[t], Andreas Huber[w], Theodorus van der Kwast[x], Eveline A. Heijnsdijk[y], Chris Bangma[b], Harry J. De Koning[y], Fritz H. Schröder[b], Anssi Auvinen[z], on behalf of the ERSPC investigators*

EUROPEAN UROLOGY 76 (2019) 43–51



NND= 18

The Göteborg 1 screening PC screening study

Mortality results from the Göteborg randomised population-based prostate-cancer screening trial

Jonas Hugosson, Sigrid Carlsson, Gunnar Aus, Svante Bergdahl, Ali Khatami, Pär Lodding, Carl-Gustaf Pihl, Johan Stranne, Erik Holmberg, Hans Lilja

THE JOURNAL of UROLOGY®
www.auajournals.org/journal/juro

OPEN

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

Jonas Hugosson, Rebecka Arnsrud Godtman, Sigrid V. Carlsson, Gunnar Aus, Anna Grenabo Bergdahl, Pär Lodding, Carl-Gustaf Pihl, Johan Stranne, Erik Holmberg & Hans Lilja

To cite this article: Jonas Hugosson, Rebecka Arnsrud Godtman, Sigrid V. Carlsson, Gunnar Aus, Anna Grenabo Bergdahl, Pär Lodding, Carl-Gustaf Pihl, Johan Stranne, Erik Holmberg & Hans Lilja (2018) 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, Scandinavian Journal of Urology, 52:1, 27-37, DOI: 10.1080/21681805.2017.1411392

Results from 22 years of Followup in the Göteborg Randomized Population-Based Prostate Cancer Screening Trial

Maria Frånlund,[1] Marianne Månsson,[1] Rebecka Arnsrud Godtman,[1] Gunnar Aus,[2] Erik Holmberg,[3] Karin Stinesen Kollberg,[1] Pär Lodding,[1] Carl-Gustaf Pihl,[4] Johan Stranne,[1] Hans Lilja[5,6,7,8] and Jonas Hugosson[1]*

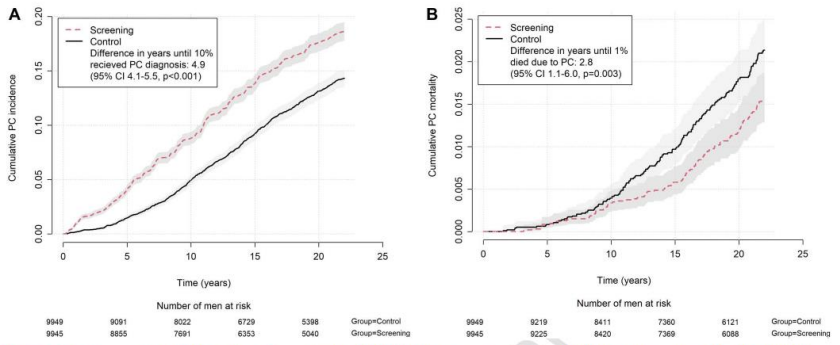


Figure 2. *A*, observed PC incidence up to December 31, 2016 19,894). *B*, observed PC mortality up to December 31, 2016 (19,894).

NNI=217

NND= 9

Prostate cancer mortality in various age groups
In men < 80 years the mortality has declined 32% !!

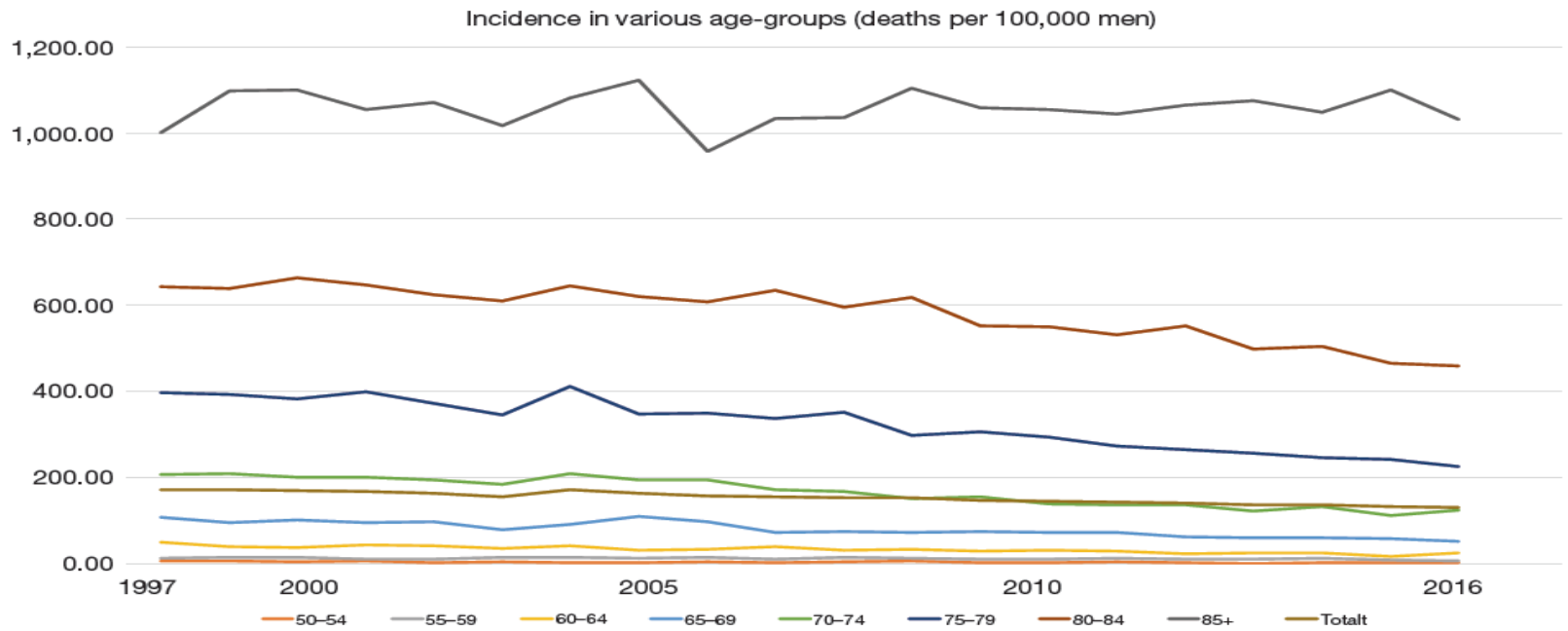


Figure 2 Mortality in various age groups from 1997 to 2016 in Sweden expressed as number of PC deaths per 100,000 men per age category. PC, prostate cancer.

Incidence in Sweden in various age groups

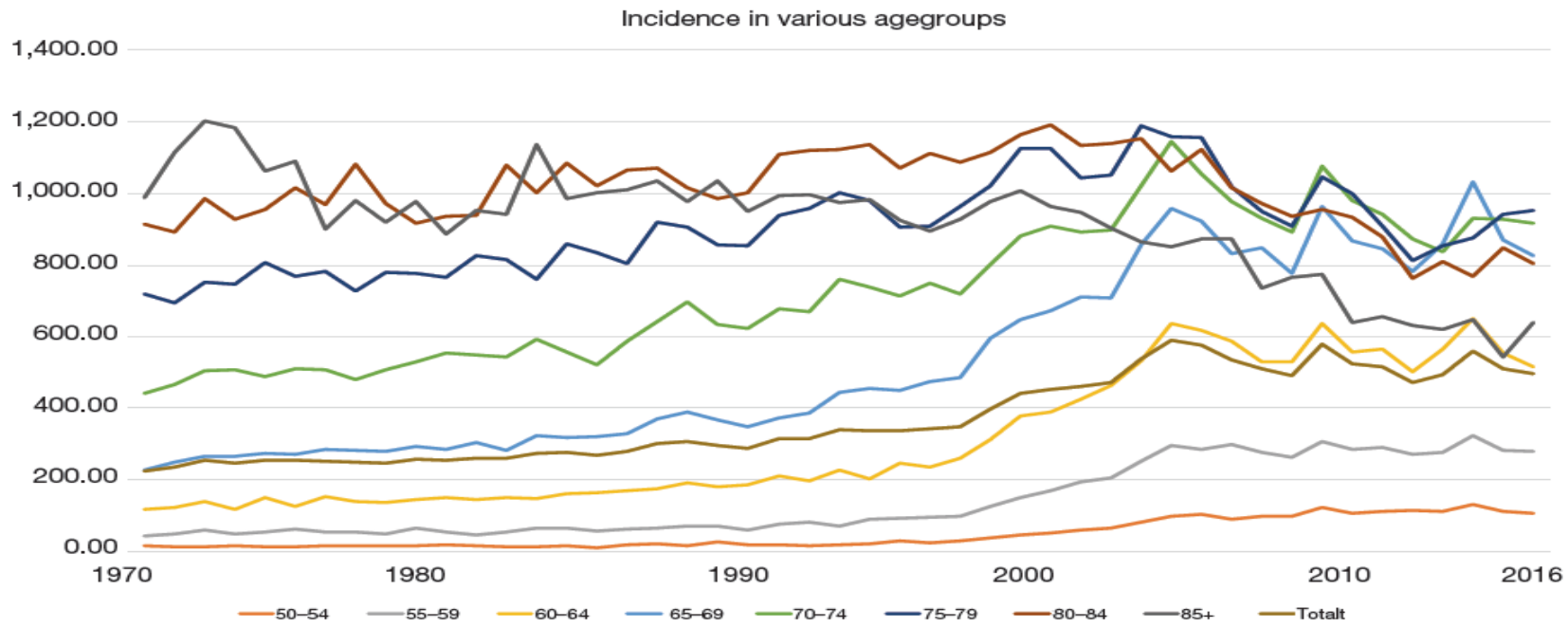


Figure 1 Incidence in various age groups from 1970 to 2016 in Sweden expressed as number per 100,000 men per age category.

Frikostig PSA testning och systematiska blinda biopsier innebär flera saker förutom att fler dödliga PC hittas i tid

- Vi hittar PC som är indolenta i stor omfattning
- Även potentiellt dödlig PC kan många gånger ha ett långt förlopp som gör att många män inte hinner utveckla sjukdomen pga konkurrerande dödsorsaker

- Detta är vad vi kallar överdiagnostik som leder till att vi gör friska män till cancer patienter helt i onödan för resten av livet
- Leder ofta till överbehandling som medför risk för bestående biverkningar med nedsatt livskvalitet som följd

The benefits with a clear stage shift and accompanying PC mortality reduction is outweighted by the high rate of over-diagnosis

Table 2. *Risk group classification and primary treatment of cancers detected*

	CG (1,124 PC detected)										SG (1,528 PC detected)									
	All PC		Low Risk PC		Intermediate Risk		High Risk		Advanced		All PC		Low Risk PC		Intermediate Risk		High Risk		Advanced	
No. pts	1,114*		269		434		206		136		1,528†		723		510		174		89	
No. primary treatment (%):																				
Prostatectomy	329	(30)	95	(35)	162	(37)	34	(16)	8	(6)	549	(36)	232	(32)	236	(46)	54	(31)	9	(10)
Radiation	118	(11)	11	(4)	43	(10)	52	(25)	2	(1)	118	(8)	40	(6)	47	(9)	30	(17)	0	
Surveillance	388	(35)	158	(59)	177	(41)	27	(13)	0		662	(43)	440	(61)	191	(37)	21	(12)	0	
Endocrine treatment	268	(24)	5	(2)	48	(11)	91	(44)	122	(89)	184	(12)	4	(1)	33	(6)	66	(38)	79	(89)
Unknown	11	(1)	0		4	(1)	2	(1)	4	(4)	15	(1)	7	(1)	3	(1)	2	(1)	1	(1)
Median yrs age at diagnosis (IQR)	69 (65, 73)		67 (63, 70)		69 (66, 73)		70 (66, 75)		69 (65, 74)		66 (63, 69)		65 (62, 68)		67 (64, 70)		69 (65, 76)		71 (66, 77)	
No. T3, T4 PC (%)	–		–		–		69	(33)	81	(60)	–		–		–		67	(39)	58	(65)
No. PC deaths	156		1		22		48		82		112		3		19		31		55	

Low risk—T1, not N1 or M1, and GS ≤6 and PSA <10 ng/ml. Intermediate risk—T1-2, but not N1 or M1, with a GS ≤7, PSA <20 ng/ml or both; and not meeting the criteria for low risk. High risk—T1-4, but not N1 or M1, with a GS >8, PSA <100 ng/ml or both; and not meeting the criteria for low or intermediate risk. Advanced—N1 or M1, or PSA >100 ng/ml. Unknown—includes 11 cases detected at autopsy.

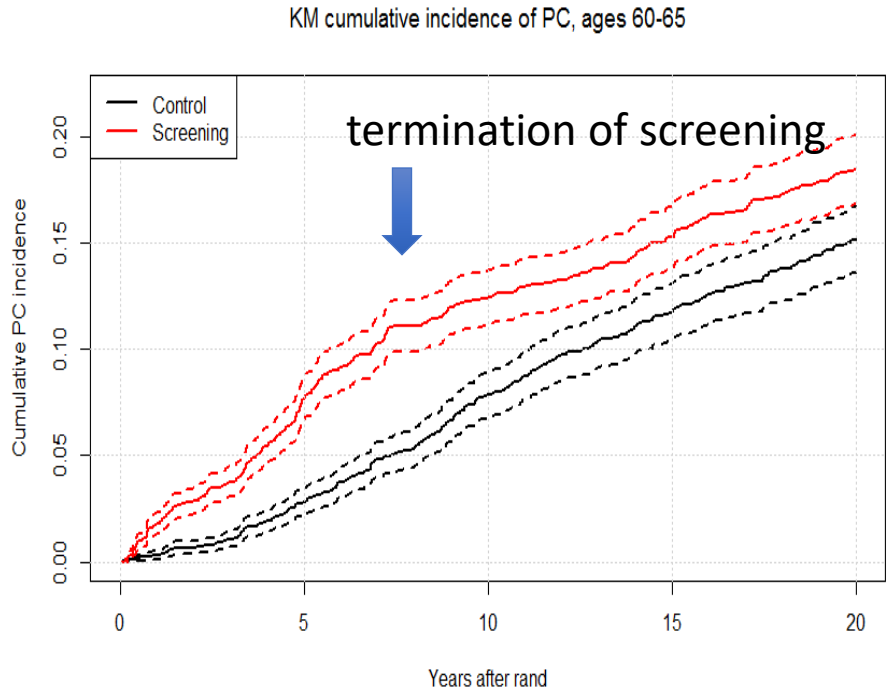
* Ten men had no treatment (detected on autopsy) and 69 men had unknown risk group in the CG; 5 men who died from PC had an unknown risk group.

† In the SG 32 men had unknown risk group; 18 men had prostatectomy, 1 man had radiation, 11 surveillance and 2 men had endocrine treatment.

47 % är lågrisk cancer I G1 studiens screeningarm

Improving PC screening is mainly achieved by reducing the high rate of over-diagnosis! But this must be obtained by an algorithm that still detects cancers in a curable stage.

Incidence of PC after termination of screening compared to that in the control group



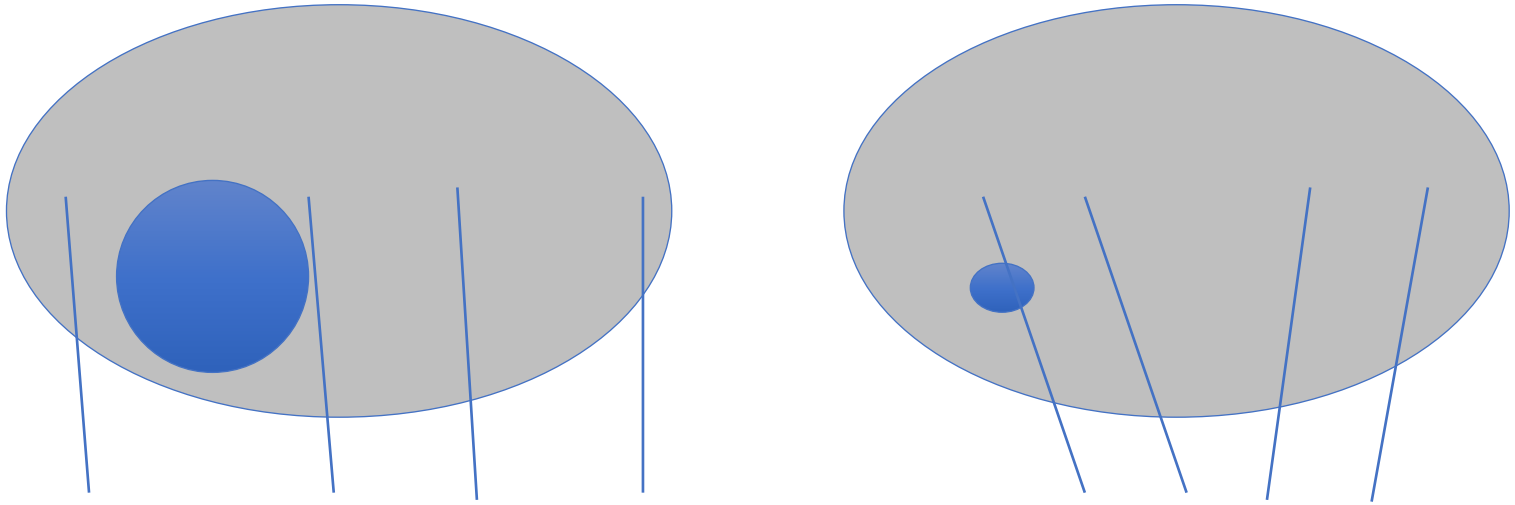
The long term incidence after termination of screening in the screening group remain at 3-4 % higher level compared to the control group indicating that one third of men with screen-detected cancers are are truly over diagnosed they will not develop clinical PC within reasonable time, non-progressive cancers

Konklusioner

1. Cirka hälften av de cancrar vi hittar vid PSA screening med systematiska biopsier kommer aldrig att utvecklas till klinisk cancer
2. Dödlig prostatacancer är sannolikt oftast en relativt snabbt förlöpande sjukdom, för att hitta dessa i tid behövs ett ganska intensivt screening program
3. Kan vi identifiera potentiellt dödlig prostatacancer från den ofarliga, och helst undvika att diagnosticera den, MR???

Reason for over-diagnosis

Current biopsy technique is blind!! Until recently the standard algorithm in men with PSA elevation was systematic 10-14 core-biopsies spread in the gland



Kan MR och riktade biopsier minska risken för diagnostik av indolent PC?

- Hypotesen är då att ”farlig” PC syns på MR och små indolenta cancrar syns ej.

BJUI
BJU INTERNATIONAL

Role of magnetic resonance imaging before initial biopsy: comparison of magnetic resonance imaging–targeted and systematic biopsy for significant prostate cancer detection

Jérémie Haffner*, Laurent Lemaitre†, Philippe Puech†, Georges-Pascal Haber§, Xavier Leroy†, J. Stephen Jones§ and Arnauld Villers*

*Department of Urology, †Department of Radiology and †Department of Pathology, Université Lille Nord de France, F-59000 Lille, France; INSERM, U703, F-59120 Loos, France; CHU Lille, F-59000 Lille, France, and §Glickman Urological & Kidney Institute CCF, USA

Accepted for publication 26 November 2010

- 555 pts who had a pre biopsy mpMRI
- All had 12 systematic + possible targeted bx
- 302 PC detected
- 249 (82%) were classified as significant

- 63 % had pos MRI
- Systematic biopsies detected 237 significant and 53 non significant cancers
- Targeted biopsies detected 236 significant and none of the non significant cancers

Some cancers are missed with MRI and some with systematic biopsies

Diagnostic accuracy of multi-parametric MRI and TRUS biopsy in prostate cancer (PROMIS): a paired validating confirmatory study

Hashim U Ahmed, Ahmed El-Shater Bosaily*, Louise C Brown*, Rhian Gabe, Richard Kaplan, Mahesh K Parmar, Yolanda Collaco-Moraes, Katie Ward, Richard G Hindley, Alex Freeman, Alex P Kirkham, Robert Oldroyd, Chris Parker, Mark Emberton, and the PROMIS study group†*

	MP-MRI, % (95% CI)	TRUS-biopsy, % [95% CI]	Test ratio* [95% CI]	p value
Primary definition (Gleason score ≥4+3 or cancer core length ≥6 mm), prevalence of clinically significant cancer 230 (40%, 36–44%)				
Sensitivity test	93 (88–96)	48 (42–55)	0·52 (0·45–0·60)	p<0·0001
Specificity test	41 (36–46)	96 (94–98)	2·34 (2·08–2·68)	p<0·0001
PPV	51 (46–56)	90 (83–94)	8·2 (4·7–14·3)	p<0·0001
NPV	89 (83–94)	74 (69–78)	0·34 (0·21–0·55)	p<0·0001
Secondary definition (Gleason score ≥3+4 or cancer core length ≥4 mm), prevalence of clinically significant cancer 331 (57%, 53–62%)				
Sensitivity test	87 (83–90)	60 (55–65)	0·69 (0·64–0·76)	p<0·0001
Specificity test	47 (40–53)	98 (96–100)	2·11 (1·85–2·41)	p<0·0001
PPV	69 (64–73)	98 (95–100)	22·7 (8·6–59·9)	p<0·0001
NPV	72 (65–79)	65 (60–70)	0·70 (0·52–0·96)	p=0·025
Any Gleason score 7 (≥3+4), prevalence of clinically significant cancer 308 (53%, 49–58%)				
Sensitivity test	88 (84–91)	48 (43–54)	0·55 (0·49–0·62)	p<0·0001
Specificity test	45 (39–51)	99 (97–100)	2·22 (1·94–2·53)	p<0·0001
PPV	65 (60–69)	99 (95–100)	40·8 (10·2–162·8)	p<0·0001
NPV	76 (69–82)	63 (58–67)	0·53 (0·38–0·73)	p<0·0001

Prevalence of disease on TPM-biopsy, N (%, 95% CI) *McNemar test to compare sensitivity and specificity present ratio of proportions. TPM-biopsy=template prostate mapping biopsy. MP-MRI=multi-parametric-MRI. TRUS-biopsy=transrectal ultrasound-guided prostate biopsy. PPV=positive predictive value. NPV=negative predictive value. General Estimating Equation logistic regression model to compare PPV and NPV present odds ratios. All ratios presented as TRUS relative to MRI.

***Table*: Diagnostic accuracy of TRUS-biopsy and MP-MRI in the detection of clinically significant prostate cancer using alternative secondary definitions of clinically significant cancer**

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 10, 2018 VOL. 378 NO. 19

MRI-Targeted or Standard Biopsy for Prostate-Cancer Diagnosis

V. Kasivisvanathan, A.S. Rannikko, M. Borghi, V. Panebianco, L.A. Mynderse, M.H. Vaarala, A. Briganti, L. Budäus, G. Hellawell, R.G. Hindley, M.J. Roobol, S. Eggener, M. Ghei, A. Villers, F. Bladou, G.M. Villeirs, J. Virdi, S. Boxler, G. Robert, P.B. Singh, W. Venderink, B.A. Hadaschik, A. Ruffion, J.C. Hu, D. Margolis, S. Crouzet, L. Klotz, S.S. Taneja, P. Pinto, I. Gill, C. Allen, F. Giganti, A. Freeman, S. Morris, S. Punwani, N.R. Williams, C. Brew-Graves, J. Deeks, Y. Takwoingi, M. Emberton, and C.M. Moore, for the PRECISION Study Group Collaborators*

Table 2. **Comparison of Cancer Detection between Groups.***

Outcome	MRI-Targeted Biopsy Group (N=252)	Standard-Biopsy Group (N=248)	Difference†	P Value
Biopsy outcome — no. (%)			—	—
No biopsy because of negative result on MRI	71 (28)	0		
Benign tissue	52 (21)	98 (40)		
Atypical small acinar proliferation	0	5 (2)		
High-grade prostatic intraepithelial neoplasia	4 (2)	10 (4)		
Gleason score				
3+3	23 (9)	55 (22)		
3+4	52 (21)	35 (14)		
3+5	2 (1)	1 (<1)		
4+3	18 (7)	19 (8)		
4+4	13 (5)	6 (2)		
4+5	7 (3)	2 (1)		
5+5	3 (1)	1 (<1)		
No biopsy‡	4 (2)	3 (1)		
Withdrawal from trial§	3 (1)	13 (5)		
Clinically significant cancer¶				
Intention-to-treat analysis — no. (%)	95 (38)	64 (26)	12 (4 to 20)	0.005
Modified intention-to-treat analysis — no./total no. (%)	95/245 (39)	64/235 (27)	12 (3 to 20)	0.007
Per-protocol analysis — no./total no. (%)	92/235 (39)	62/227 (27)	12 (3 to 20)	0.007
Clinically insignificant cancer — no. (%)	23 (9)	55 (22)	−13 (−19 to −7)	<0.001
Maximum cancer core length — mm	7.8±4.1	6.5±4.5	1.0 (0.0 to 2.1)	0.053
Core positive for cancer — no./total no. of cores (%)	422/967 (44)	515/2788 (18)	—	—
Men who did not undergo biopsy — no. (%)‖	78 (31)	16 (6)	—	—

MRI seems beneficial in clinical patients but does it work for screening?

EURURO-6564; No. of Pages 8
ARTICLE IN PRESS
EUROPEAN UROLOGY XXX (2015) XXX–XXX

available at www.sciencedirect.com
journal homepage: www.europeanurology.com

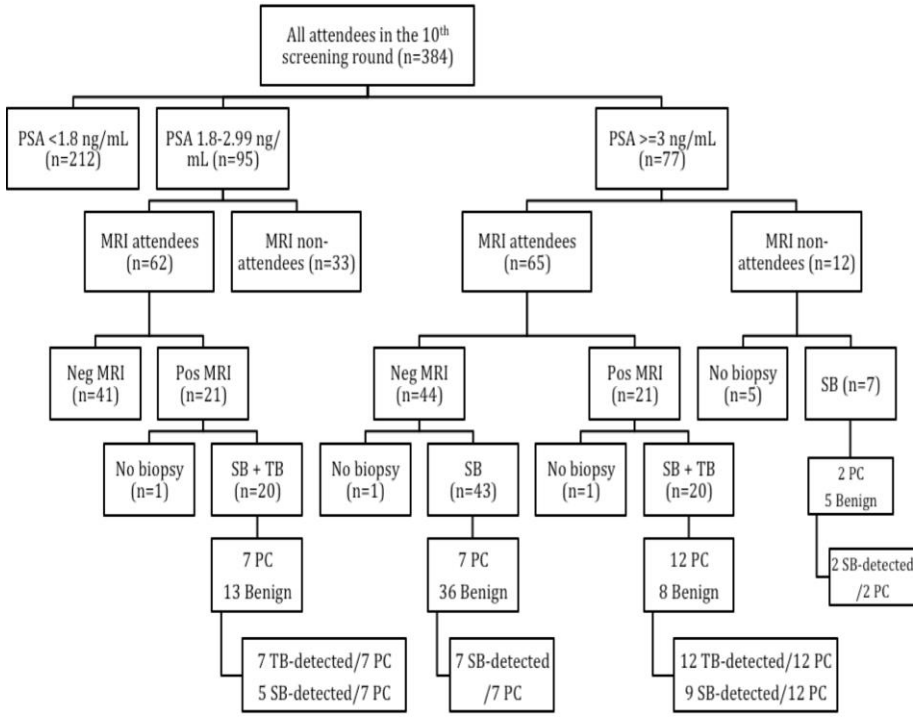
European Association of Urology

Platinum Priority – Prostate Cancer
Editorial by XXX on pp. x–y of this issue

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 Geterud[e], Ali Khatami[a], Andreas Socratous[e], Johan Stranne[a], Mikael Hellström[e], Jonas Hugosson[a]*

Figure 1.



B) Features of MRI negative cancers

	PSA	T-stage	Gleason	Biopsy mode	No. of sectors with cancer	Modified Epstein criteria
1	3.47	T1c	3+3=6	SB	1/10	IS
2	4.05	T1c	3+3=6	SB	3/10	S
3	3.53	T1c	3+3=6	SB	1/10	IS
4	3.32	T1c	3+4=7	SB	1/10	S
5	6.83	T1c	3+4=7	SB	4/10	S
6	4.04	T1c	3+3=6	SB	1/10	S
7	3.03	T1c	3+3=6	SB	1/10	IS

MRI detected 75 % of clinically significant cancers
If only men with pos MRI would have been biopsied and only with targeted directed 65 % of biopsies would have been avoided and almost all of non-significant cancers

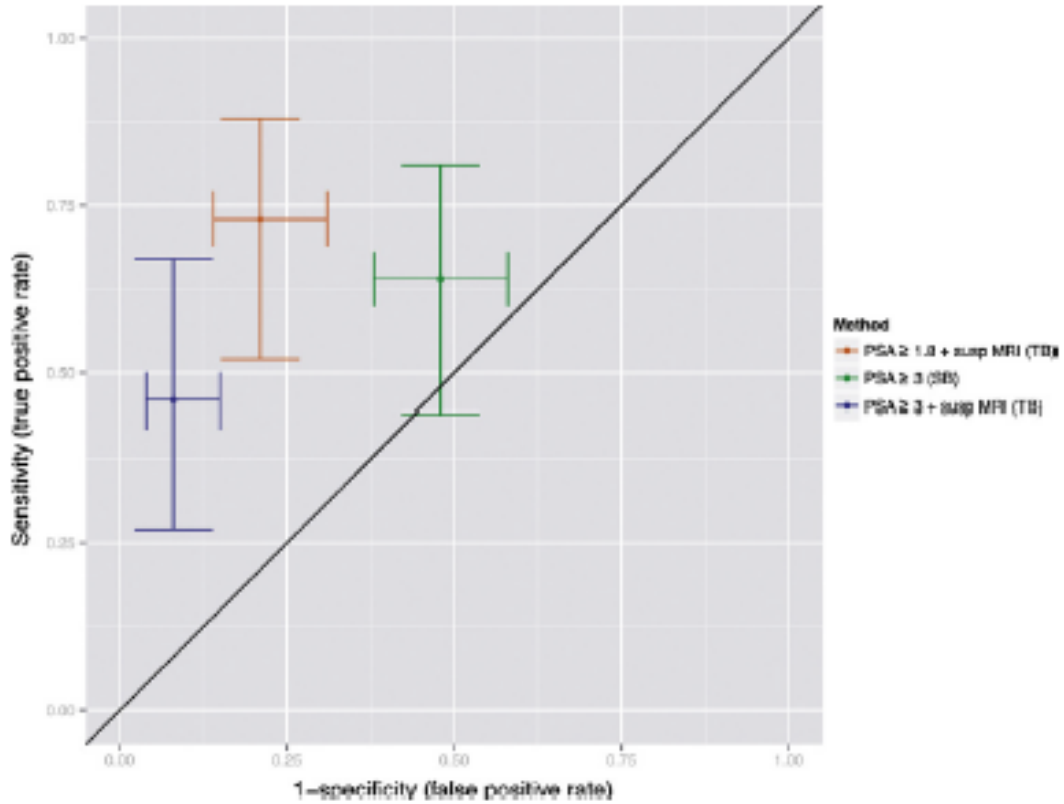


Fig. 2 – Estimated sensitivity and specificity of prostate cancer detection depending on screening strategy (prostate-specific antigen [PSA] ≥ 3 ng/ml followed by systematic biopsy, PSA ≥ 3.0 ng/ml followed by targeted biopsy, and PSA ≥ 1.8 ng/ml followed by targeted biopsy). Bars indicate 95% confidence intervals for sensitivity (y-axis) and 1-specificity (x-axis).
PSA = prostate specific antigen; Susp MRI = suspicious magnetic resonance imaging (see 'Methods' for details); SB = systematic biopsy; TB = targeted biopsy.

Randomised screeningstudies based on MRI

Randomised screening studies including MRI

STHLM 3

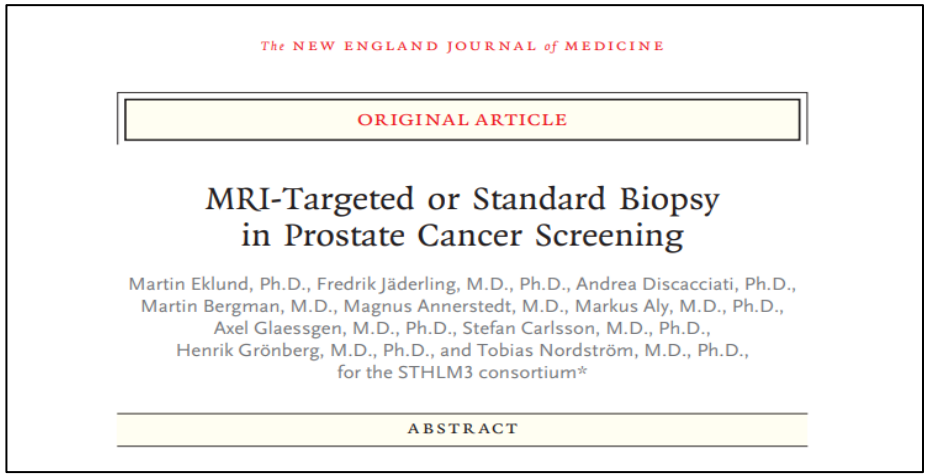
Improved Prostate Cancer Diagnostics

G2

PROBASE

Die Deutsche Prostatakrebs Screening Studie

PROSCREEN



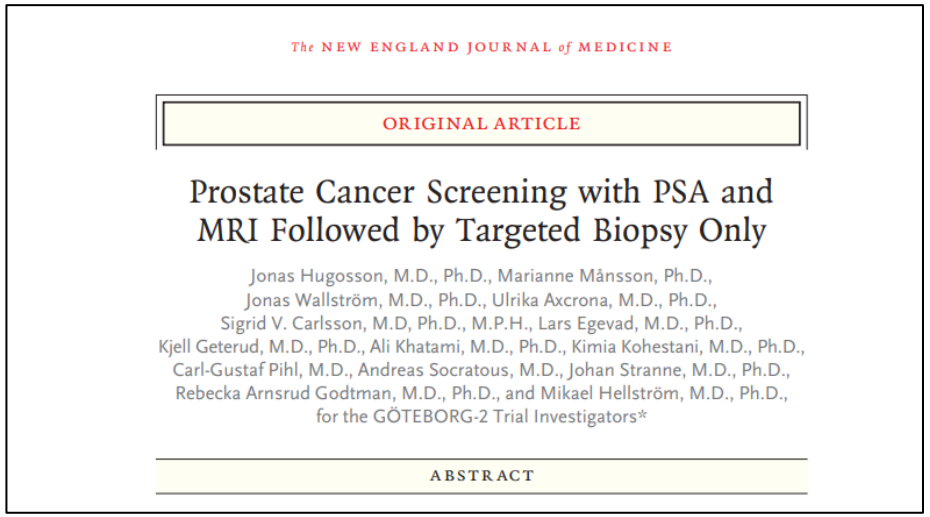
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

MRI-Targeted or Standard Biopsy in Prostate Cancer Screening

Martin Eklund, Ph.D., Fredrik Jäderling, M.D., Ph.D., Andrea Discacciati, Ph.D., Martin Bergman, M.D., Magnus Annerstedt, M.D., Markus Aly, M.D., Ph.D., Axel Glaessgen, M.D., Ph.D., Stefan Carlsson, M.D., Ph.D., Henrik Grönberg, M.D., Ph.D., and Tobias Nordström, M.D., Ph.D., for the STHLM3 consortium*

ABSTRACT



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Prostate Cancer Screening with PSA and MRI Followed by Targeted Biopsy Only

Jonas Hugosson, M.D., Ph.D., Marianne Månsson, Ph.D., Jonas Wallström, M.D., Ph.D., Ulrika Axcrona, M.D., Ph.D., Sigrid V. Carlsson, M.D, Ph.D., M.P.H., Lars Egevad, M.D., Ph.D., Kjell Geterud, M.D., Ph.D., Ali Khatami, M.D., Ph.D., Kimia Kohestani, M.D., Ph.D., Carl-Gustaf Pihl, M.D., Andreas Socratous, M.D., Johan Stranne, M.D., Ph.D., Rebecka Arnsrud Godtman, M.D., Ph.D., and Mikael Hellström, M.D., Ph.D., for the GÖTEBORG-2 Trial Investigators*

ABSTRACT

Eklund et al. NEJM 2021
Hugosson et al. NEJM 2022

Göteborg 2-studien

Hypotes: MR före bx och enbart riktade bx för män med positiv MR minskar överdiagnostiken med 50% med en bibevarad hög sensitivitet för signifikant cancer

Primärt utfallsmått: detektion av kliniskt insignifikant PC (ISUP 1/GS 3+3)

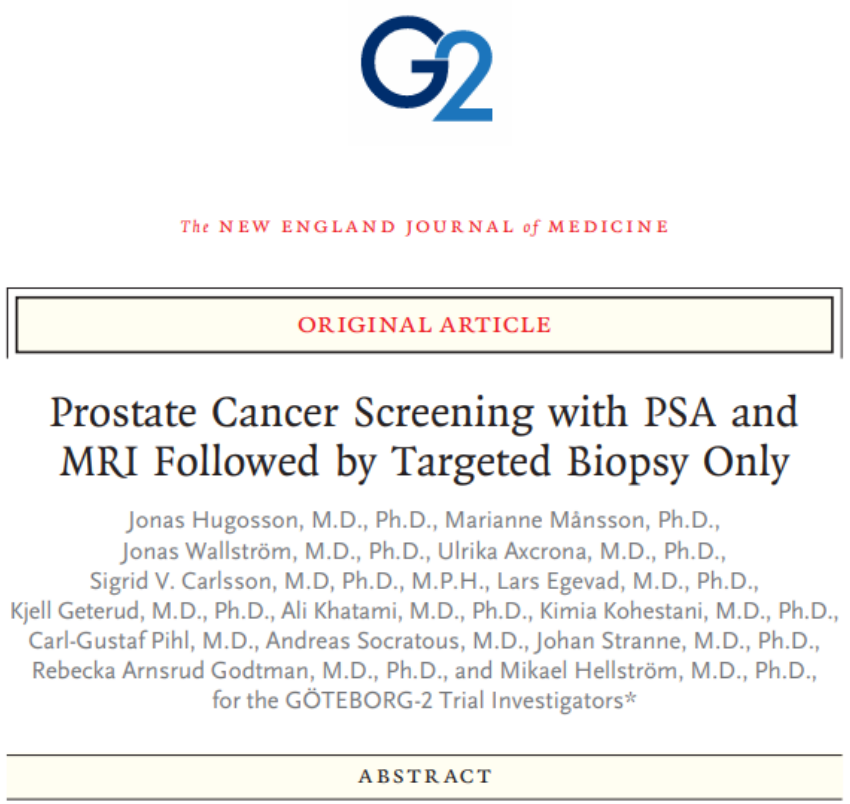
Sekundärt utfallsmått: kliniskt signifikant PC (ISUP≥2/GS ≥3+4

Multi/biparametrisk 3 T MRI (konsensusbedömning av 2 radiologer)

Kognitiva ”fusion”-biopsier

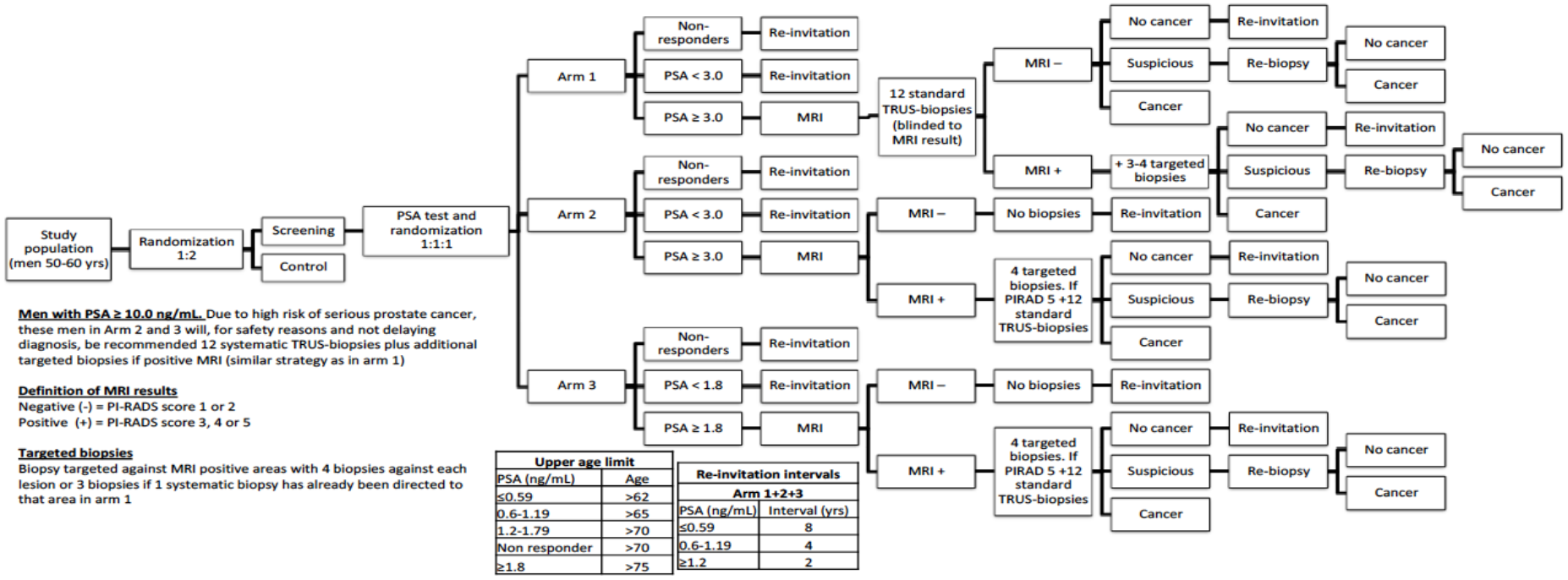
Kompletterande systematiska biopsier i arm 2 och 3 vid fynd av cancer i riktade biopsier för att undvika grading bias

Eftergranskning av PAD (3 oberoende patologers bedömning vägs samman)



Hugosson et al. NEJM 2022
Wallström et al. Eur Urol Onc. 20??

Screening algorithm G2

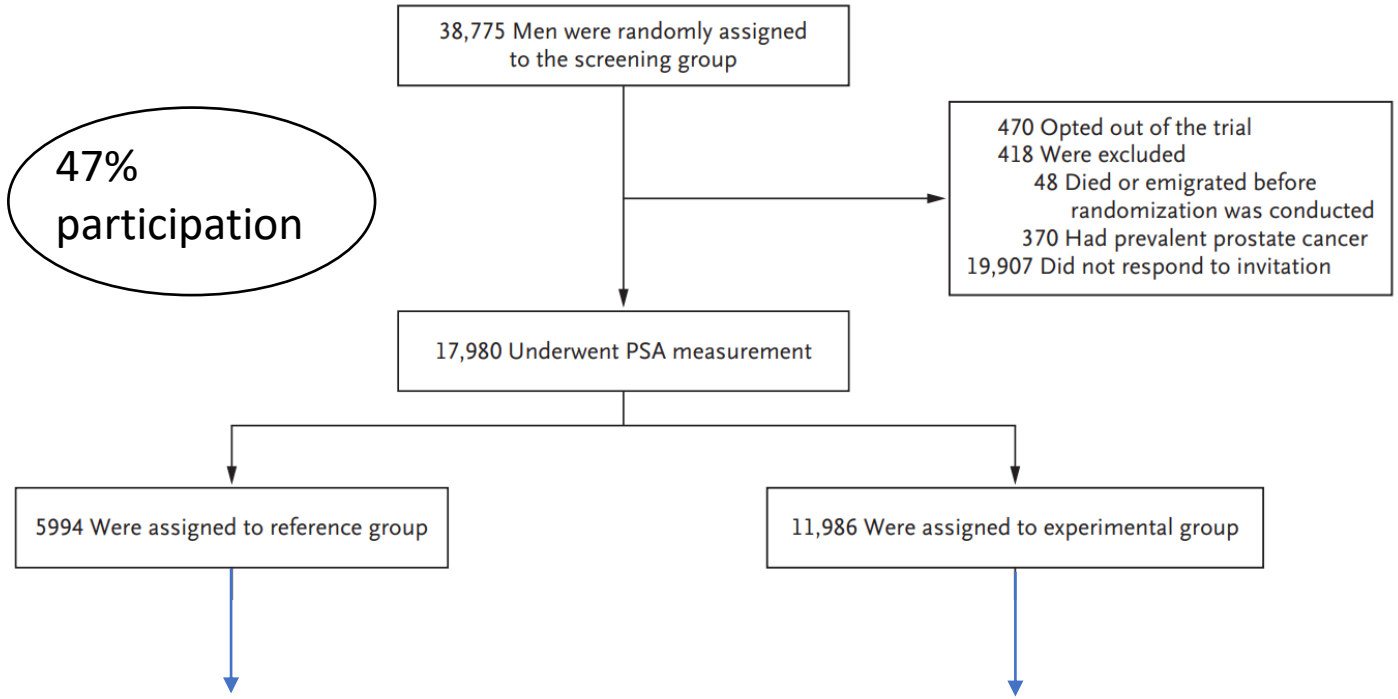


Randomisation was stopped at January 2021 and last invitation to the first round took place in April 2021
Altogether 38,775 men were randomised to the screening group and 19,000 men to the control group

Status of the G2 study 2022-04-25

	Number invited	Number of PSA tests	Number of MRI	Number of biopsies
First invitation round	37835	17971	1788	809
First participation round	-	20228		
Second invitation round	30039	8901	1655	499
Second participation round	-	8559		
Third invitation round	18537	3982	968	280
Third participation round	-	2441		
Fourth invitation round	4043	689	182	44
Fourth participation round	-	315		
Total	90454	31543	4593	1632

Population formed by the first round of invitation



Systematiska biopsier samt MR + riktade biopsier för män med PSA >= 3 ng/ml (n = 405)
Män i arm 1

Enbart MR + riktade biopsier för män med PSA >= 3 ng/ml (n = 796)
Män i arm 2 och 3

Intention To Treat (ITT):
Alla 17980 män som gjorde PSA-test (oavsett om de följt protokoll el ej)

Per Protocol (PP):
Exkludera män som inte gjorde MR och/el biopsi enligt protokoll

- Ref grupp: 70 män exkl.
  - Ej MR: 5%
  - Ej biopsi : 4% av MR pos
    20% av MR neg etc
- Exp grupp: 62 män exkl.
  - Ej MR: 4%
  - Ej biopsi: 2% av MR pos

Modified Per Protocol (ModPP):
Exkludera män ungefär som ovan

Räkna bara cancer i riktade biopsier för män med PSA ≥ 10 i experiment grupp

Table 1. Characteristics of the Participants at Randomization.*

Characteristic	Reference Group (N=5994)	Experimental Group (N=11,986)
Median age (IQR) — yr	56 (52–59)	56 (52–59)
Family history of prostate cancer — no. (%)		
Yes	630 (11)	1264 (11)
No	2754 (46)	5554 (46)
Missing data	2610 (44)	5168 (43)
Pretrial PSA test — no. (%)		
Yes	1948 (32)	3878 (32)
No	2513 (42)	5012 (42)
Missing data	1533 (26)	3096 (26)
Pretrial prostate biopsy — no. (%)		
Yes	75 (1)	170 (1)
No	4427 (74)	8806 (73)
Missing data	1492 (25)	3010 (25)
Median PSA level (IQR) — ng/ml	0.8 (0.5–1.4)	0.8 (0.5–1.4)
PSA level — no. (%)		
<3 ng/ml	5589 (93)	11,190 (93)
3 to 9.9 ng/ml	389 (6)	737 (6)
≥10 ng/ml	16 (<1)	59 (<1)

Karaktäristik samma i bägge grupperna:

- Median ålder vid rand: 56 år
- PSA innan studien: 32%
- Biopsi innan studien: 1%
- PSA
  - Median = 0.8
  - ≥ 3 ng/ml: 7%
  - ≥ 10 ng/ml: 1%

95 % av de med förhöjt PSA genomgick MR
Hos män med biopsiindikation, 85 % accepterade i referensgruppen och 90 % I experimentgruppen

Gleason 3+3 Gleason > 3+3

Resultat (ITT och primär def av insign/sign PC)

	Reference Group (N=5994)*	Experimental Group (N=11,986)	Experimental vs. Reference Group, MRI-Targeted and Systematic Biopsy
	MRI-Targeted and Systematic Biopsy	MRI-Targeted Biopsy	Relative Risk (95% CI)
PSA ≥3 ng/ml — no. (%)	405 (6.8)	796 (6.6)	
Any prostate cancer — no. (%)	140 (2.3)	176 (1.5)	0.63 (0.50 to 0.78)
Clinically insignificant cancer — no. (%)	72 (1.2)	66 (0.6)	0.46 (0.33 to 0.64)§
Clinically significant cancer — no. (%)	68 (1.1)	110 (0.9)	0.81 (0.60 to 1.10)

Primär:

Sekundär:

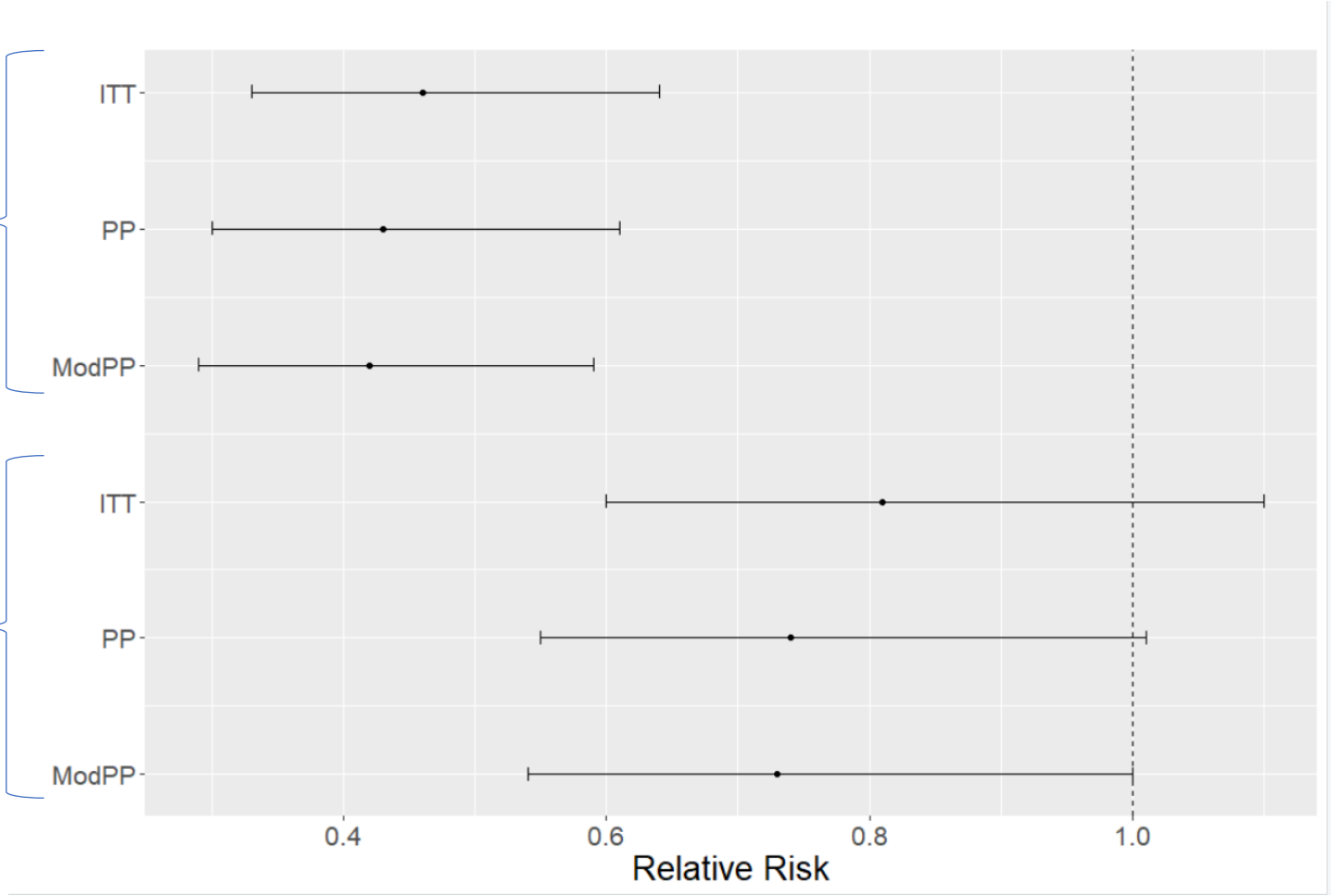
335 st MR pos

P<0.001

Per protokoll analyser

Insignifikant PC

Signifikant PC



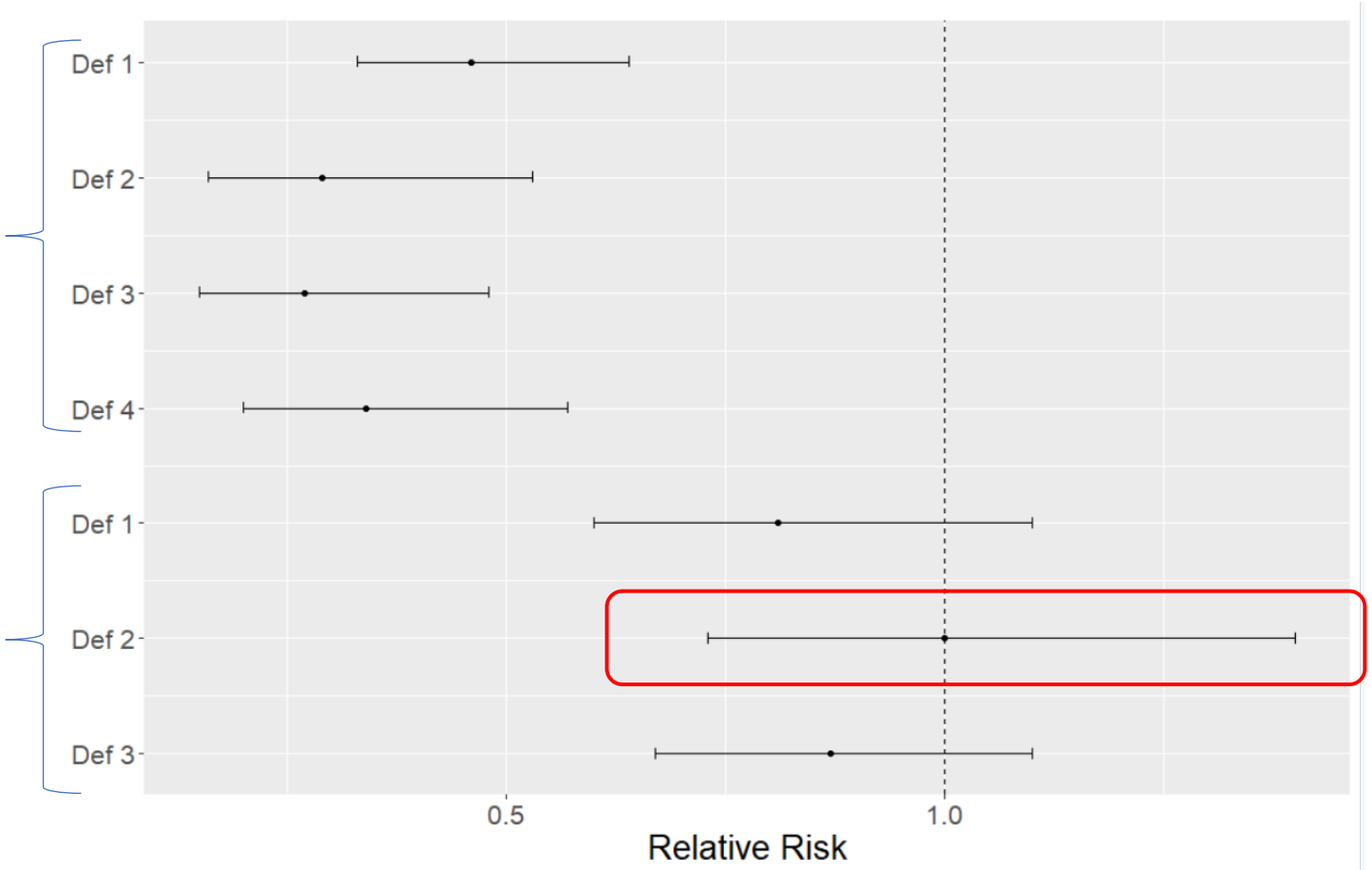
Per protocol (PP):
Exkludera män som inte gjorde MR och/el biopsi enligt protokoll (70 resp 62 män exkl)

Modified per protocol (modPP):
Ungefär som PP men räkna bara cancer i riktade biopsier för män med PSA ≥ 10 i exp grupp

Alternativa definitioner av insign and sign cancer, ITT

Insignifikant PC

Signifikant PC



Striktare def av sign PC
→ bättre resultat

Insign, Def 2: Maximum 2 sectors positive with less than 50 % involvement and Gleason score= 3+3 and unilateral involvement and PSA density < 0.15
Insign, Def 3: Tumor volume at prostatectomy specimen < 0.5 cc and Gleason 3+3, if not operated definition 2
Insign, Def 4: Tumor volume at prostatectomy specimen < 0.5 cc and Gleason not > 3+4, if not operated definition 2 including Gleason 3+4
Sign, Def 2: Maximal tumor length in a single core biopsy > 6 mm or Gleason > 3+4
Sign, Def 3: Maximal tumor length in a single core biopsy > 4 mm or Gleason > 3+3

Vilka cancrar hade missats utan systematiska biopser i referensgruppen?

- Totalt 140 PC
  - 72 st Gleason 3+3
  - 68 st > Gleason 3+3
- Upptäcktes EJ med enbart riktade biopsier mot MR positiva sektorer:
  - 44 st Gleason 3+3 (38 st MR negativa)
  - 10 st Gleason 3+4 (9 MR negativa)
    - Alla 10 var intermediate risk
    - De flesta <5% grad 4 och primär behandling var aktiv monitorering

Gleason 3+3 cancrar som detekterats med MR+rikt jämfört med systematiska biopsier

Table S5B	Detected by Systematic Biopsy Reference Group (N = 44)	Detected by MRI Targeted Biopsy Experimental Group & Reference Group (N = 85)
At least 4 millimeters of cancer in single biopsy — no. (%)	5 (11)	44 (52)
At least 6 millimeters of cancer in single biopsy — no. (%)	1 (2)	31 (36)
Unilateral cancer — no. (%)	37 (84)	57 (67)
Number of sectors with cancer — no. (%)		
1 sector	23 (52)	32 (38)
2-4 sectors	17 (39)	38 (45)
5-8 sectors	4 (9)	15 (18)
Primary treatment		
Active Surveillance — no. (%)	42 (95)	58 (68)
Radical prostatectomy or radiation therapy — no. (%)	2 (5)	26 (31)

Även med enbart MR+riktade biopsier detekteras en hel del insignifikant cancer.

Är dessa annorlunda jämfört med dem som detekterades med enbart syst biopsies?

Ja, allvarligare om upptäckta med MR + riktade biop

Enbart riktade eller riktade plus systematiska biopsier?

- Systematiska biopsier ökar risken för överdiagnostik får anses som vetenskapligt bevisat idag men två frågor kvarstår att besvara
- 1. Att en tumör som vi bedömer som signifikant inte syns på MR betyder inte att algoritmen med att avvakta biopsi är felaktig. Frågan är hur många tumörer som blir obotbara innan de syns på MR och kan dessa tumörer karakteriseras?
- 2. Ger systematiska biopsier tilläggsinformation som är så värdefull att män som har stor risk för en cancer, t ex PI-RADS 5 bör genomgå även systematiska biopsier i det diagnostiska skedet

What Are We Missing? False-Negative Cancers at Multiparametric MR Imaging of the Prostate[1]

Samuel Borofsky, MD
Arvin K. George, MD
Sonia Gaur, BS
Marcelino Bernardo, BS
Matthew D. Greer, BS
Francesca V. Mertan, BSME
Myles Taffel, MD
Vanesa Moreno, MD
Maria J. Merino, MD
Bradford J. Wood, MD
Peter A. Pinto, MD
Peter L. Choyke, MD
Baris Turkbey, MD

Purpose: To characterize clinically important prostate cancers missed at multiparametric (MP) magnetic resonance (MR) imaging.

Materials and Methods: The local institutional review board approved this HIPAA-compliant retrospective single-center study, which included 100 consecutive patients who had undergone MP MR imaging and subsequent radical prostatectomy. A genitourinary pathologist blinded to MP MR findings outlined prostate cancers on whole-mount pathology slices. Two readers correlated mapped lesions with reports of prospectively read MP MR images. Readers were blinded to histopathology results during prospective reading. At histopathologic examination, 80 clinically unimportant lesions (<5 mm; Gleason score, 3+3) were excluded. The same two readers, who were not blinded to histopathologic findings, retrospectively reviewed cancers missed at MP MR imaging and assigned a Prostate Imaging Reporting and Data System (PI-RADS) version 2 score to better understand false-negative lesion characteristics. Descriptive statistics were used to define patient characteristics, including age, prostate-specific antigen (PSA) level, PSA density, race, digital rectal examination results, and biopsy results before MR imaging. Student *t* test was used to determine any demographic differences between patients with false-negative MP MR imaging findings and those with correct prospective identification of all lesions.

Results: Of the 162 lesions, 136 (84%) were correctly identified with MP MR imaging. Size of eight lesions was underestimated. Among the 26 (16%) lesions missed at MP MR imaging, Gleason score was 3+4 in 17 (65%), 4+3 in one (4%), 4+4 in seven (27%), and 4+5 in one (4%). Retrospective PI-RADS version 2 scores were assigned (PI-RADS 1, $n = 8$; PI-RADS 2, $n = 7$; PI-RADS 3, $n = 6$; and PI-RADS 4, $n = 5$). On a per-patient basis, MP MR imaging depicted clinically important prostate cancer in 99 of 100 patients. At least one clinically important tumor was missed in 26 (26%) patients, and lesion size was underestimated in eight (8%).

Conclusion: Clinically important lesions can be missed or their size can be underestimated at MP MR imaging. Of missed lesions, 58% were not seen or were characterized as benign findings at second-look analysis. Recognition of the limitations of MP MR imaging is important, and new approaches to reduce this false-negative rate are needed.

[1] From the Molecular Imaging Program (S.B., S.G., M.B., M.D.G., F.V.M., P.L.C., B.T.), Urologic Oncology Branch (A.K.G.), and Laboratory of Pathology (V.M., M.J.M.), National Cancer Institute, National Institutes of Health, 10 Center Dr, Room B3B85, Bethesda, MD 20892; Department of Radiology, George Washington University Hospital, Washington, DC (S.B., M.T., P.A.P.); and Center for Interventional Oncology, National Cancer Institute, and Department of Radiology and Imaging Sciences, Clinical Center, National Institutes of Health, Bethesda, Md (B.J.W.). Received January 26, 2016; revision requested March 14; revision received June 5, 2017; accepted June 27; final version accepted April 28. **Address correspondence to** B.T. (e-mail: *turkbeyi@mail.nih.gov*).

80 clinically non important cancers were excluded

Significant cancers were defined as cancers > 5mm

Double reading with experinced radiologists

84 % of clinically important cancers were correctly identified

MRI detected clinically important cancers in 99 out of 100 patients

Table 3

Properties of Lesions Missed at MR Imaging

Feature	No. of Lesions ($n = 26$)
Location	
Peripheral zone	16 (62)
Transition zone	10 (38)
Level	
Apex	12 (46)
Mid	12 (46)
Base	2 (8)
Gleason score	
3+3	0 (0)
3+4	17 (65)
4+3	1 (4)
4+4	7 (27)
4+5	1 (4)
PI-RADS version 2 score	
1	8 (31)
2	7 (27)
3	6 (23)
4	5 (29)
5	0 (0)

Note.—Data in parentheses are percentages.

Conclusion

- There are not enough data yet that could answer the question how dangerous it is to delay the diagnosis in men with a negative MRI and if subgroups of men with high risk could be identified by PSAD and/or markers such as Stockholm 3 and others
- The G2 trial is designed to evaluate this by comparing arm 1 and 2. The comparison will focus upon the rate of high risk and advanced cancers that appear either as interval cancers or at follow-up screens. The first report will be carried out on our data up to 22-06-30 and will hopefully be published within a year

Hur skall bilddiagnostiken utvecklas inom PC diagnostiken?

- Dagens diagnostik grundar sig på PSA, MR och biopsier
- Kan biopsier vara skadliga och om möjligt undvikas?
- Kan ny bilddiagnostik säkerställa diagnos i så hög grad att biopsi kan undvikas?

Kan MR övervakning utan biopsi bli ett alternativ?

- Vem vet?
- Förekommer vid annan cancer, t ex små njurtumörer
- PSA surveillance är för trubbigt, krävs upprepad biopsi vid AM
- Hur farligt är biopsi?

Risker med prostatabiopsi

- Obehagligt för patienten, i G2 studien tycker majoriteten att biopsier är smärtsamma och i stora studier sjunker biopsifrekvensen markant med lång uppfljningstid hos män som står på aktiv monitorering.
- Falskt negativa resultat
- Falskt positiva resultat, förekommer knappast
- Infektion, allvarlig infektion hos 2-4 %
- Bidrar till resistensutveckling, en tablett Ciprofloxacin ger förändrad tarmflora med ökad Cipro resistens i upp till 1 år
- Kan biopsi sprida cancer? Varför har 90 % av de som utvecklar PSA relaps efter operation omätbart PSA vid första kontrollen och det kan ta väldigt många år innan relapsen kommer?

Papers in Press. Published October 10, 2019 as doi:10.1373/clinchem.2019.310912
The latest version is at http://clinchem.aaccjnls.org/cgi/doi/10.1373/clinchem.2019.310912

Clinical Chemistry 66:1
000–000 (2020)

Cancer Diagnostics

Tumor-Associated Release of Prostatic Cells into the Blood after Transrectal Ultrasound-Guided Biopsy in Patients with Histologically Confirmed Prostate Cancer

Simon A. Joosse,[1] Burkhard Beyer,[2†] Christin Gasch,[1†] Paulina Nastały,[1†] Andra Kuske,[1†] Hendrik Isbarn,[2] Ludwig J. Horst,[1] Claudia Hille,[1] Tobias M. Gorges,[1] Laure Cayrefourcq,[3] Catherine Alix-Panabières,[3] Pierre Tennstedt,[4] Sabine Riethdorf,[1] Thorsten Schlomm,[2] and Klaus Pantel[1*]

Blodprov för kvantitativ analys av cirkulerande Tumörceller togs omedelbart före och 30 minuter efter mellannåls biopsier (8-12 stycken) hos 115 män med prostatacancermisstanke

Table 1. Characteristics of the total cohort of participants.[a]

	PCa– (n = 40)	PCa+ (n = 75)	Total (n = 115)	*P value*
Age at diagnosis, years (mean)	40–82 (61.4)	46–79 (66.1)	40–82 (64.5)	0.0086
Total PSA, ng/mL (median)	1.9–13.4 (7.1)	2.5–304.6 (7.7)	1.9–304.6 (7.7)	0.0586
Free PSA, ng/mL (median)	0.2–2.8 (1.1)	0.2–3.2 (0.9)	0.2–3.2 (0.9)	0.2438
Free PSA/total PSA ratio, % (median)	7.8–25.9 (14.9)	2.2–35.6 (10.8)	2.2–35.6 (12.9)	<0.001
Gleason score				
3 + 3		n = 24		
3 + 4		n = 26		
4 + 3		n = 5		
≥4 + 4		n = 20		
T stage				
T1		n = 10		
T2		n = 34		
T3		n = 20		
Treatment				
Prostatectomy		n = 46		
Prostatectomy + other		n = 7		
Radiotherapy		n = 13		
Other/none		n = 9		

[a] Significant test for mean: Welch 2-sample *t*-test; significant test for median: Wilcoxon rank-sum test with continuity correction.

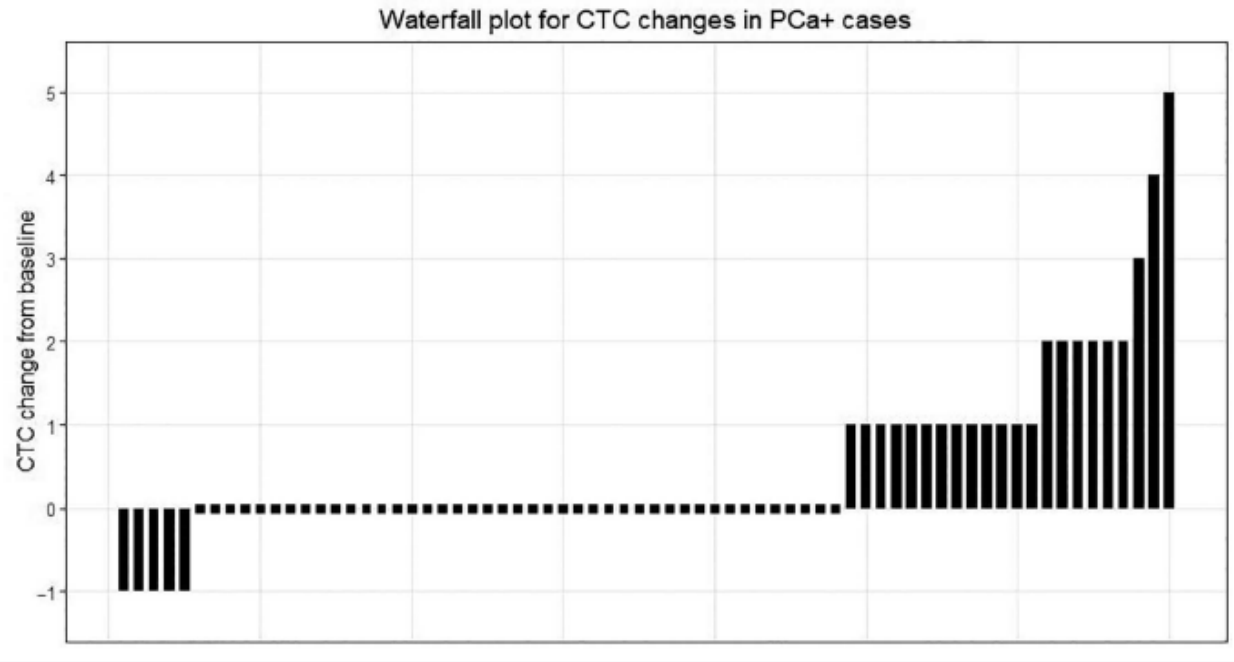


Fig. 1. CTC change.
Waterfall plot showing the change of CTCs after biopsy compared with baseline for the PCa+ cases.

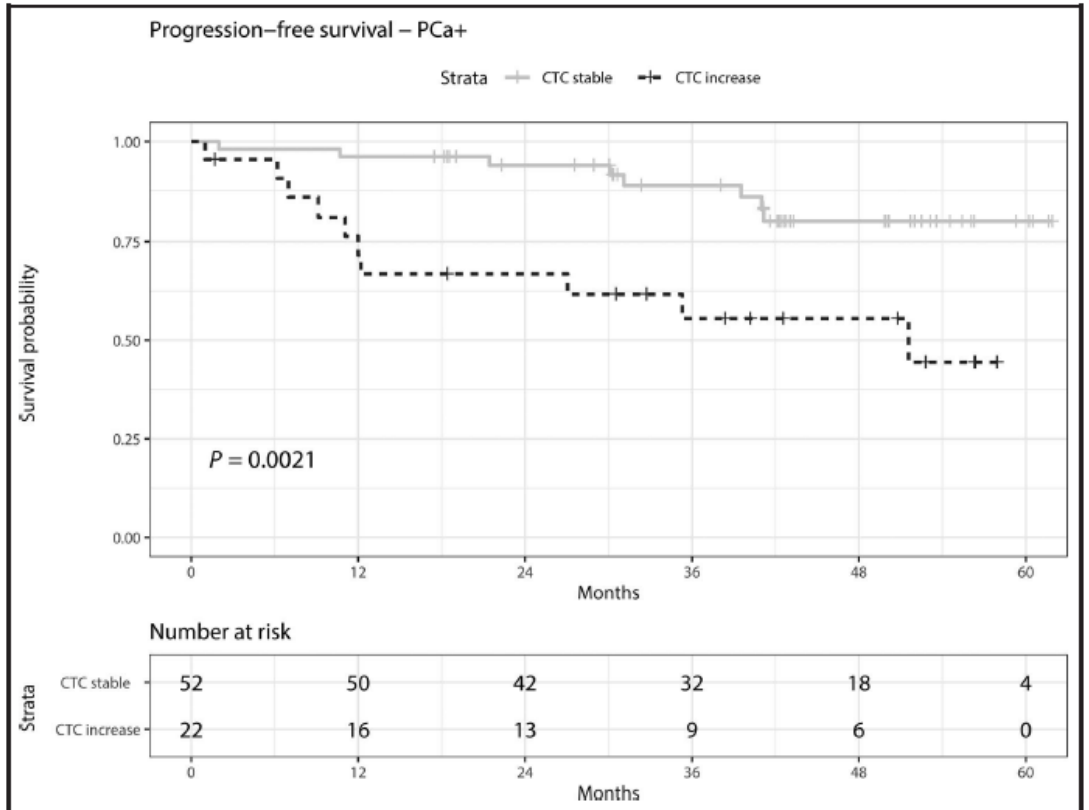


Fig. 2. Progression-free survival probability.
Kaplan–Meier function for biochemical and metastatic relapse in months (median, 41.1) correlated to increase or stable count of tumor cells after biopsy ($P = 0.0021$, log-rank test).

Table 3. Cox proportional HRs.[a]

	Univariable analysis				Multivariable analysis			
Covariate	Coefficient (b_i)	HR [exp(b_i)]	HR 95% CI	*P* value	Coefficient (b_i)	HR [exp(b_i)]	HR 95% CI	*P* value
CTC increase	1.384	3.989	1.57–10.14	0.0036	2.520	12.429	3.178–48.604	0.0003
Age	0.011	1.011	0.953–1.073	0.7190	−0.003	0.997	0.875–1.136	0.9660
PCa-positive cores	1.0375	2.822	0.50–16.04	0.2420	2.536	12.636	0.66–241.62	0.0920
PSA	0.006	1.006	0.994–1.014	0.1190	−0.077	0.925	0.850–1.007	0.0707
Gleason score (3 + 3)								
3 + 4	−0.744	0.475	0.119–1.901	0.2930	−1.825	0.161	0.027–0.976	0.0470
4 + 3	0.449	1.567	0.316–7.769	0.5830	1.090	2.976	0.194–45.549	0.4334
≥4 + 4	0.419	1.520	0.448–4.734	0.4700	−0.176	0.839	0.148–4.763	0.8429
Treatment	0.604	1.828	0.625–5.3	0.271	1.486	4.420	0.863–22.630	0.0745

[a] Estimated coefficients of progress-free survival on PCa+ individuals. Calculated are the corresponding HR, 95% CI of the HR, and *P* value in univariable and multivariable Cox proportional hazards analysis for CTC number increase after biopsy, age, the fraction of PCa+ cores, PSA at time of diagnosis, Gleason scores with 3 + 3 as reference, and prostatectomy vs radiotherapy as treatment covariate.

Ny planerad studie i Göteborg

- Hypotes; PSMA PET MR identifierar med hög specificitet en primärtumör i prostata och behov av biopsi kan därmed uppskjutas
- Inklusion; Män med PI-RADS 1-2 med hög PSA densitet som har indikation för biopsi enligt vårdprogram samt män med Pi-RADS 3 och 4
- Metod. Männen gör enligt standard först PSA och biparametrisk MR. Efter acceptans att delta i studien utförs en F-18-PSMA-1007 PET MR. Därefter går patienten till sedvanlig biopsi med antingen enbart systematiska biopsier (PI-RADS 1-2) eller systematiska plus riktade (PI-RADS 3 och 4)
- Biopsiresultaten är referensmetod vartemot NaF PET MR resultaten jämförs
- 50 patienter ingår en pilot och om safety OK så planeras ytterligare 150 patienter inkluderas

Tack för ordet