Memorial Sloan Kettering Cancer Center

20-7983. Decision-analytic modeling study of the PRECISION trial: does pre-biopsy MRI do more good than harm?

Andrew Vickers

Department of Epidemiology and Biostatistics

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Financial Relationships

Commercial Interest:	Nature of Relationship:
Opko	Stock options for advisory board participation
Arctic partners	Royalties for 4Kscore invention
Steba	Consulting

Off Label Discussion:
None

Level I evidence in favor of MRI

The NEW ENGLAND JOURNAL of MEDICINE

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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*

ABSTRACT

BACKGROUND

Multiparametric magnetic resonance imaging (MRI), with or without targeted biopsy, is an alternative to standard transrectal ultrasonography–guided biopsy for prostate-cancer detection in men with a raised prostate-specific antigen level who have not undergone biopsy. However, comparative evidence is limited.

METHODS

In a multicenter, randomized, noninferiority trial, we assigned men with a clinical

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Kasivisvanathan at the Division of Surgery and Interventional Science, UCL, 3rd Fl., Charles Bell House, 43-45 Foley St., London W1W 7TS, United Kingdom, or at veeru.kasi@ucl.ac.uk.

More high-grade, fewer low-grade with MRI

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

Not quite level I, but still New England Journal of Medicine

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

MRI-Targeted, Systematic, and Combined Biopsy for Prostate Cancer Diagnosis

M. Ahdoot, A.R. Wilbur, S.E. Reese, A.H. Lebastchi, S. Mehralivand, P.T. Gomella, J. Bloom, S. Gurram, M. Siddiqui, P. Pinsky, H. Parnes, W.M. Linehan, M. Merino, P.L. Choyke, J.H. Shih, B. Turkbey, B.J. Wood, and P.A. Pinto

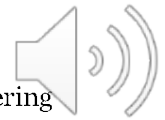
ABSTRACT

BACKGROUND

The use of 12-core systematic prostate biopsy is associated with diagnostic inaccuracy that contributes to both overdiagnosis and underdiagnosis of prostate cancer. Biopsies performed with magnetic resonance imaging (MRI) targeting may reduce the misclassification of prostate cancer in men with MRI-visible lesions.

METHODS

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Pinto at the National Cancer Institute, 10 Center Dr., Bldg. 10, Rm. 2W-5940, Bethesda, MD 20892, or at pintop@mail.nih.gov.



MRI finds many aggressive cancers that TRUS misses

No. of Patients (%) in Grade Group with Systematic Biopsy

No. of Patients (%) in Grade Group with Targeted Biopsy	No cancer	1	2	3	4	5	Total
No cancer	791 (37.6)	163 (7.8)	56 (2.7)	5 (0.2)	3 (0.1)	1 (0.05)	1019 (48.5)
1	74 (3.5)	157 (7.5)	50 (2.4)	6 (0.3)	2 (0.1)	0 (0)	289 (13.7)
2	75 (3.6)	93 (4.4)	178 (8.5)	14 (0.7)	10 (0.5)	0 (0)	370 (17.6)
3	22 (1.0)	19 (0.9)	36 (1.7)	22 (1.0)	9 (0.4)	0 (0)	108 (5.1)
4	29 (1.4)	19 (0.9)	33 (1.6)	25 (1.2)	98 (4.7)	11 (0.5)	215 (10.2)
5	8 (0.4)	3 (0.1)	6 (0.3)	1 (0.05)	15 (0.7)	69 (3.3)	102 (4.9)
Total	999 (47.5)	454 (21.6)	359 (17.1)	73 (3.5)	137 (6.5)	81 (3.9)	2103 (100.0)

Upgrading by targeted biopsy

Upgrading by both biopsy methods

Upgrading by systematic biopsy

More high-grade, fewer low-grade with MRI. Could that be reassignment?

Outcome	MRI-Targeted Biopsy Group (N=252)	Standard-Biopsy Group (N=248)	Difference†	P Value
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Clinically significant cancer¶				
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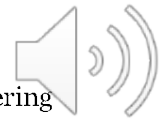
Type of cancer	MRI	TRUS
Indolent	23	55
Aggressive	95	64
Total	**118**	**119**



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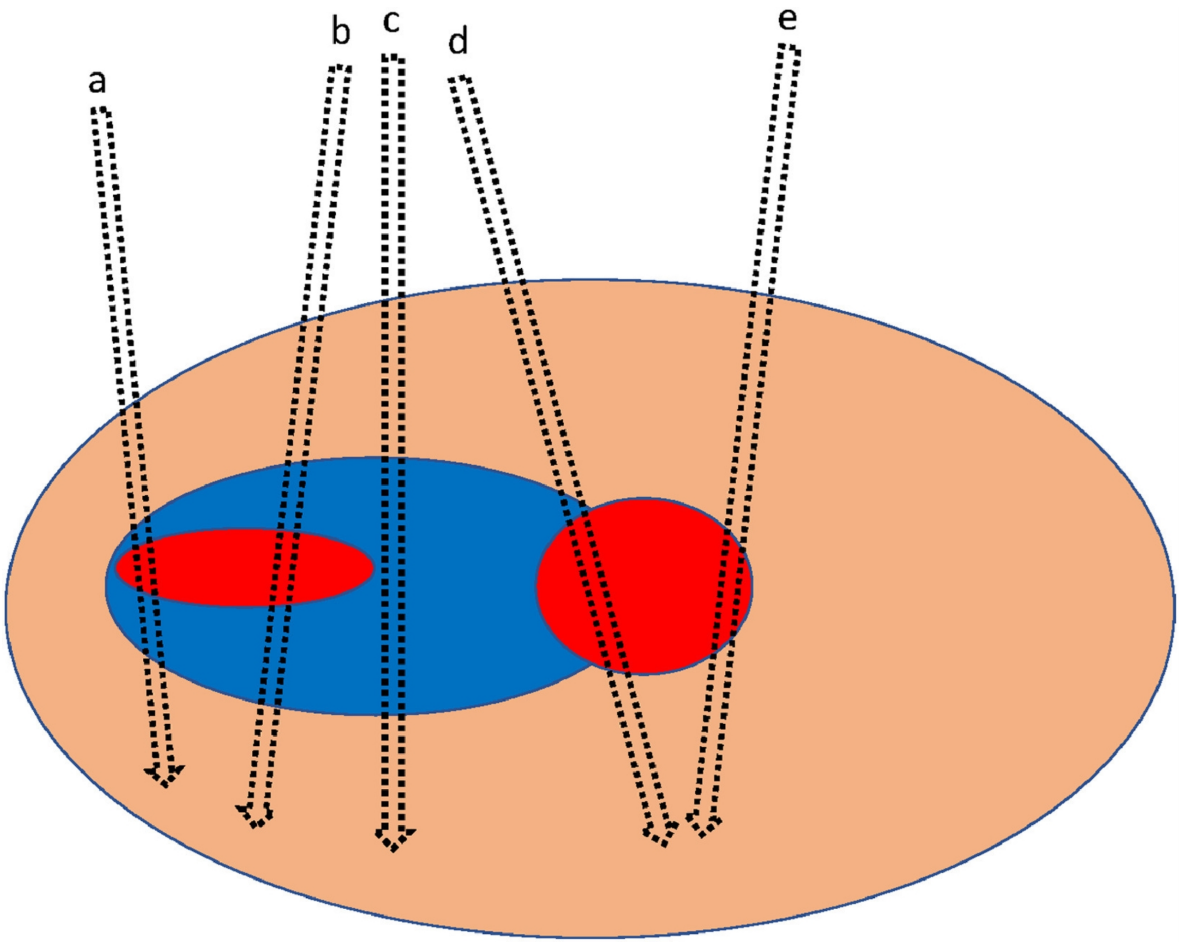
Multiple needles in MRI lead to upgrading



Are cancers missed by TRUS aggressive?

	No cancer
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4	29 (1.4)
5	8 (0.4)
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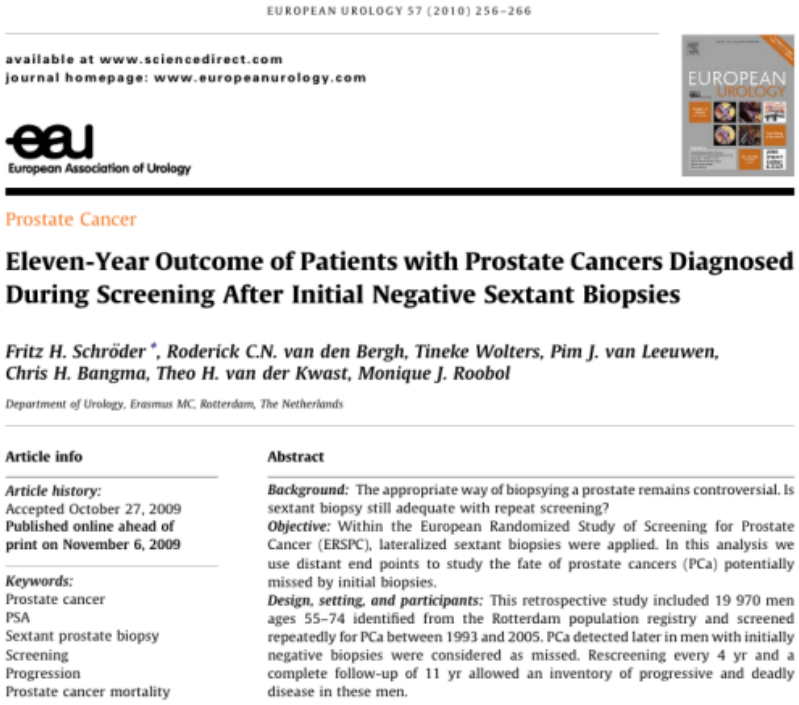

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European Association of Urology

Prostate Cancer

Eleven-Year Outcome of Patients with Prostate Cancers Diagnosed During Screening After Initial Negative Sextant Biopsies

*Fritz H. Schröder *, Roderick C.N. van den Bergh, Tineke Wolters, Pim J. van Leeuwen, Chris H. Bangma, Theo H. van der Kwast, Monique J. Roobol*

Department of Urology, Erasmus MC, Rotterdam, The Netherlands

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Progression
Prostate cancer mortality

Abstract

Background: The appropriate way of biopsying a prostate remains controversial. Is sextant biopsy still adequate with repeat screening?
Objective: Within the European Randomized Study of Screening for Prostate Cancer (ERSPC), lateralized sextant biopsies were applied. In this analysis we use distant end points to study the fate of prostate cancers (PCa) potentially missed by initial biopsies.
Design, setting, and participants: This retrospective study included 19 970 men ages 55–74 identified from the Rotterdam population registry and screened repeatedly for PCa between 1993 and 2005. PCa detected later in men with initially negative biopsies were considered as missed. Rescreening every 4 yr and a complete follow-up of 11 yr allowed an inventory of progressive and deadly disease in these men.

0.03% deaths at 11 years

Diagnose >200, treat > 100 to prevent <1 death?

High profile studies likely had different endpoints in each group

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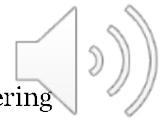
Upgrading by targeted biopsy
Upgrading by both biopsy methods
Upgrading by systematic biopsy



Modelling study step 1: create scoring schemes

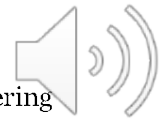
TRUS and MRI detectable cancers of equal but low oncologic risk

	TRUS					
MRI	Benign	GG 1	GG 2	GG 3	GG 4	GG 5
-ve MRI	1	6	8	4	-2	-8
Benign	0	5	7	3	-3	-9
GG 1	-5	0	11	9	6	X
GG 2	-7	-11	0	0	0	X
GG 3	-3	-9	0	0	0	0
GG 4	3	-6	0	0	0	0
GG 5	9	-3	0	0	0	0

Modelling study step 1: create scoring schemes

TRUS detectable cancers of higher oncologic risk

	TRUS					
MRI	Benign	GG 1	GG 2	GG 3	GG 4	GG 5
-ve MRI	1	6	0	-8	-20	-32
Benign	0	5	-1	-9	-21	-33
GG 1	-5	0	7	3	-3	X
GG 2	-7	-11	0	0	0	X
GG 3	-3	-9	0	0	0	0
GG 4	3	-6	0	0	0	0
GG 5	9	-3	0	0	0	0



All scoring schemes

Missed TRUS cancer high oncologic risk	Missed TRUS cancer moderate oncologic risk
TRUS and MRI equal	TRUS and MRI equal
TRUS detectable cancers > MRI	TRUS detectable cancers > MRI
TRUS detectable cancers >> MRI	

Counterfactuals: unknown for the PRECISION study

Outcome	MRI-Targeted Biopsy Group (N=252)	Standard-Biops Group (N=248)
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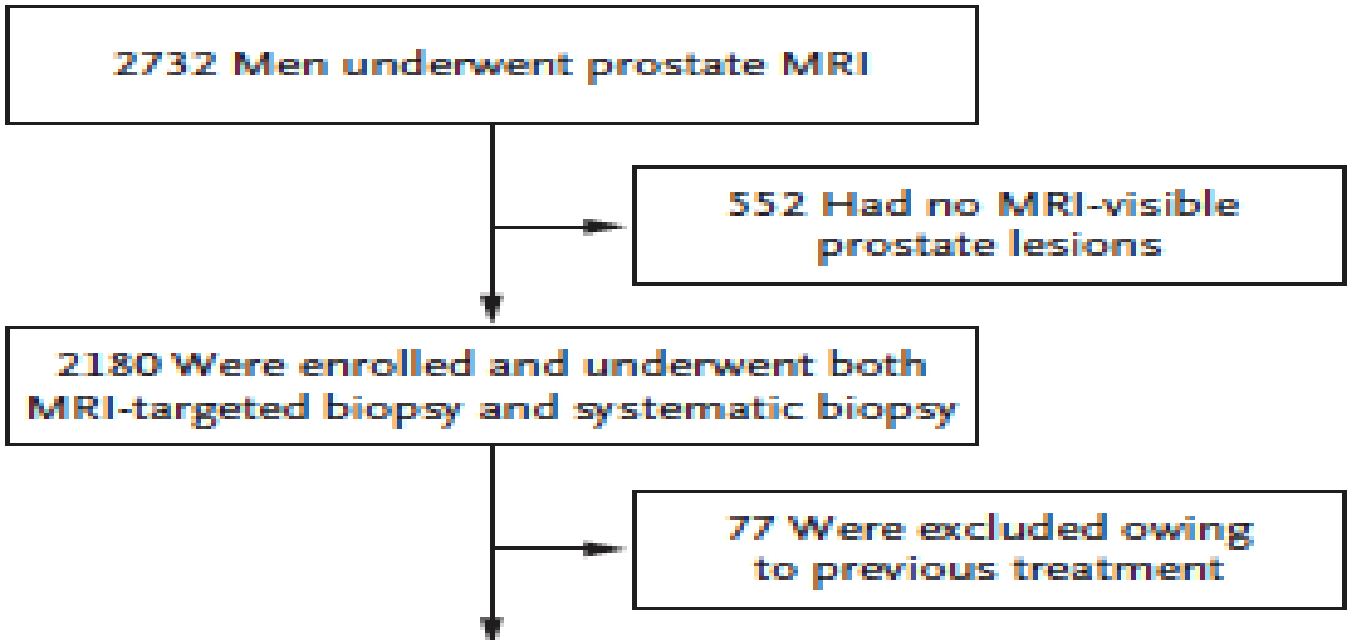
Clinically significant cancer¶		
Intention-to-treat analysis — no. (%)	95 (38)	64 (26)

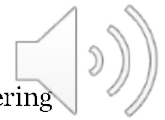
	TRUS						
MRI	Benign	GG 1	GG 2	GG 3	GG 4	GG 5	Total
-ve MRI							28.84%
Benign							22.78%
GG 1							9.28%
GG 2							21.28%
GG 3							7.26%
GG 4							6.44%
GG 5							4.1[illegible]
Total	48.75%	23.72%	15.09%	8.13%	3.02%	1.29%	100%

NCI study: unknown TRUS grade for men with negative MRI



Five scenarios for the counterfactuals

- PRECISION
  - MRI hi-grade from TRUS benign
  - MRI hi-grade from TRUS lo-grade
  - Reclassification from adjacent grades
  - Two different distributions for MRI negative
- Adhoot
  - Two different distributions for MRI negative



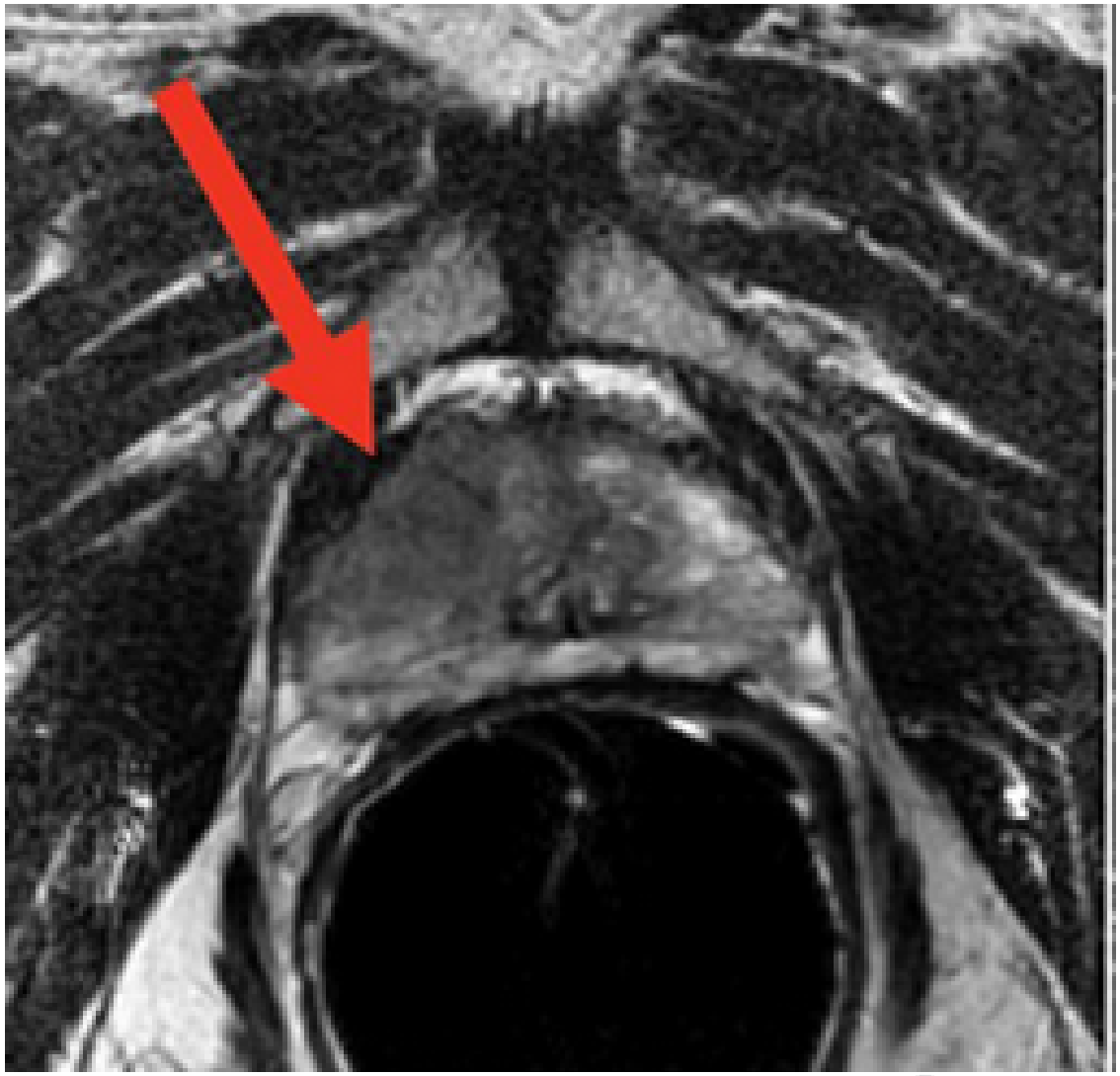
NCI study: unknown TRUS grade for men with negative MRI

	Negative Biopsy	GG1	GG2	GG3	GG4	GG5
Favorable PPV	70%	25%	4%	1%	0.25%	0.25%
Realistic PPV	80%	10%	7%	2%	1%	1%

Scoring Scheme	1: Missing a high-grade cancer harmful, equally for MRI and TRUS	2: Missing a TRUS high-grade cancer harmful, less so for MRI high-grade	3: Missing a TRUS high-grade cancer harmful, a little less so for MRI high-grade	4: Missing high-grade cancer moderately harmful, equal for TRUS and MRI	5: Missing high-grade cancer moderately harmful, less so for MRI high-grade
PRECISION					
A					
1	0.762	-0.435	0.158	-0.220	-0.514
2	0.864	-0.548	0.153	-0.134	-0.486
3	0.648	-0.521	0.061	-0.232	-0.517
B					
1	0.329	-0.793	-0.236	-0.580	-0.845
2	0.592	-0.734	-0.070	-0.308	-0.640
3	0.517	-0.495	0.007	-0.210	-0.460
Adhoot					
Favorable NPV for MRI	0.843	-0.012	0.416	0.396	0.181
Realistic NPV for MRI	0.630	-0.227	0.202	0.300	0.[illegible]

- Assume that high-grade tumors found by MRI but missed by TRUS are very harmful (conventional wisdom), then MRI of benefit
- In all other scenarios:
  - PRECISION results: MRI is either harmful or of trivial benefit
  - Adhoot results: MRI is of value in some scenarios only if we use a very favorable NPV for MRI

MRI has an obvious clinical role



Conclusions

- Recent high-profile studies appear to support MRI in prostate biopsy
- Meaning of endpoints may vary between arms
- MRI of benefit only under restrictive and unrealistic assumptions of relative harms of TRUS and MRI detectable cancers