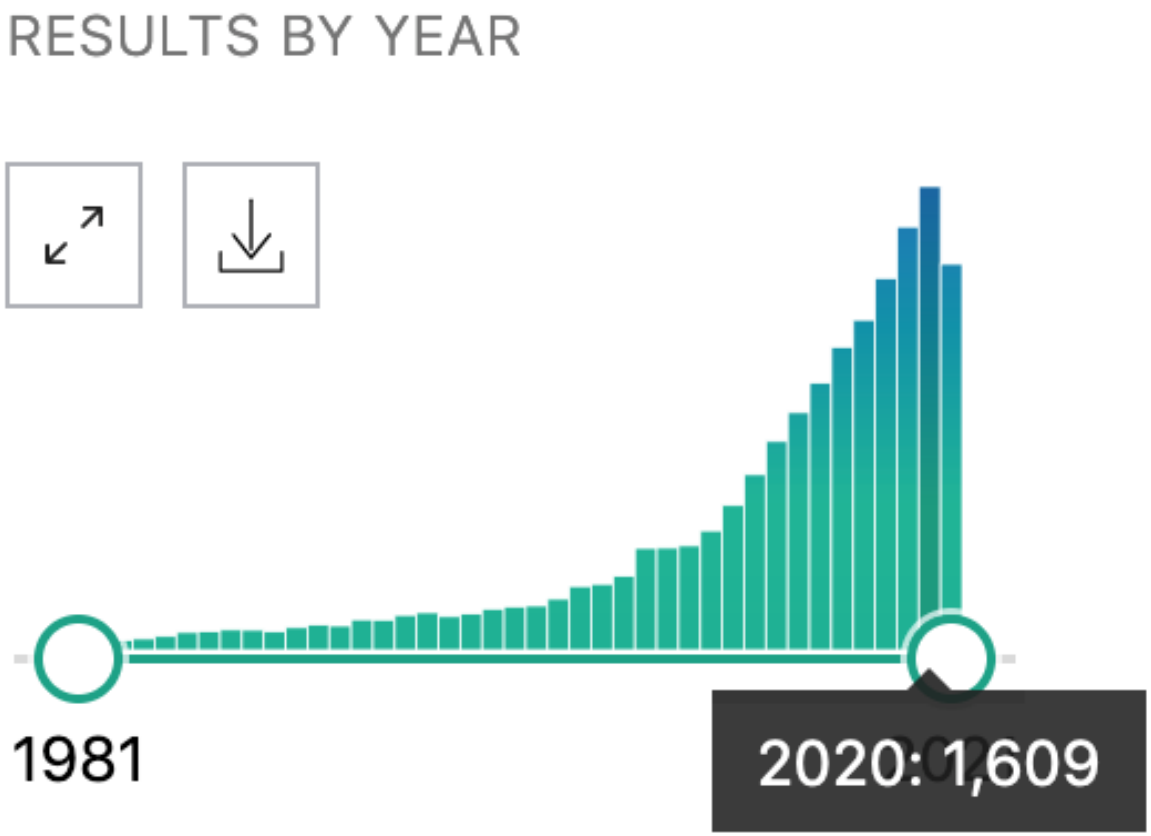
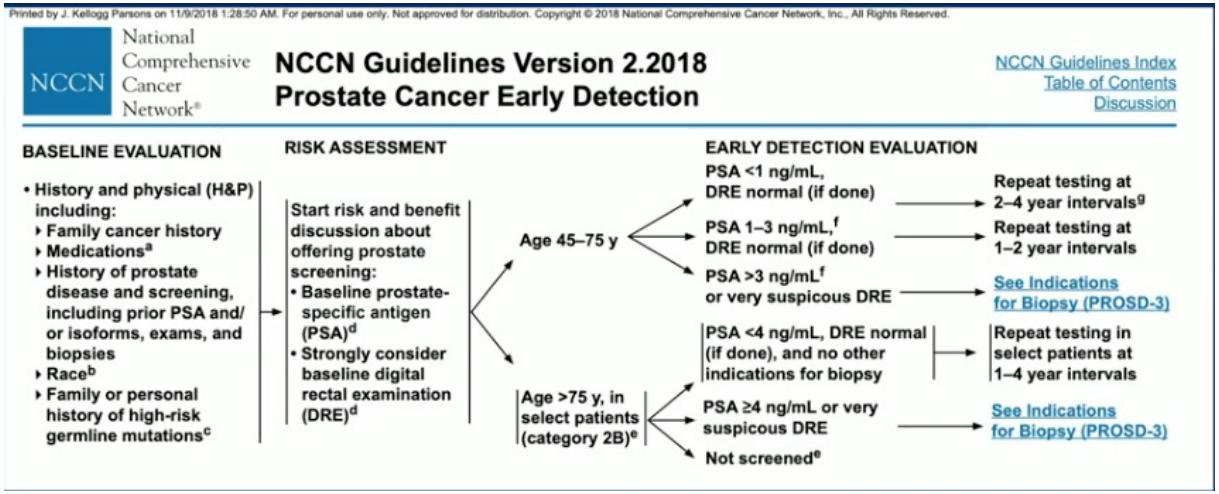
MRI is incredibly good at finding prostate cancer. But is that actually a good thing?

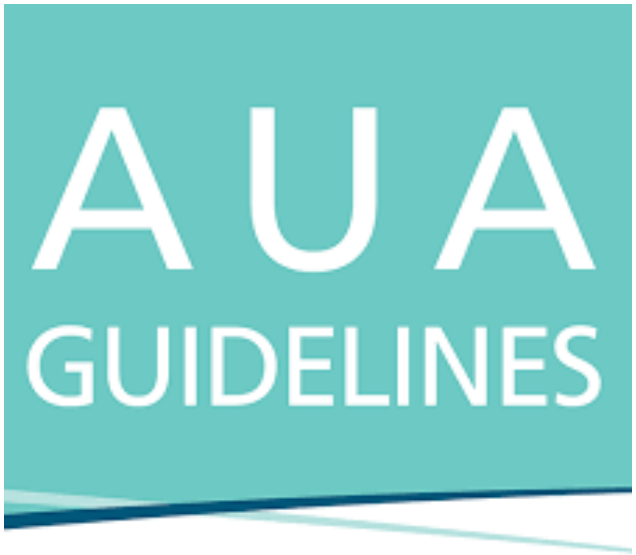
Andrew Vickers
Department of Epidemiology and Biostatistics
Memorial Sloan Kettering Cancer Center

Huge increase in interest in Prostate MRI

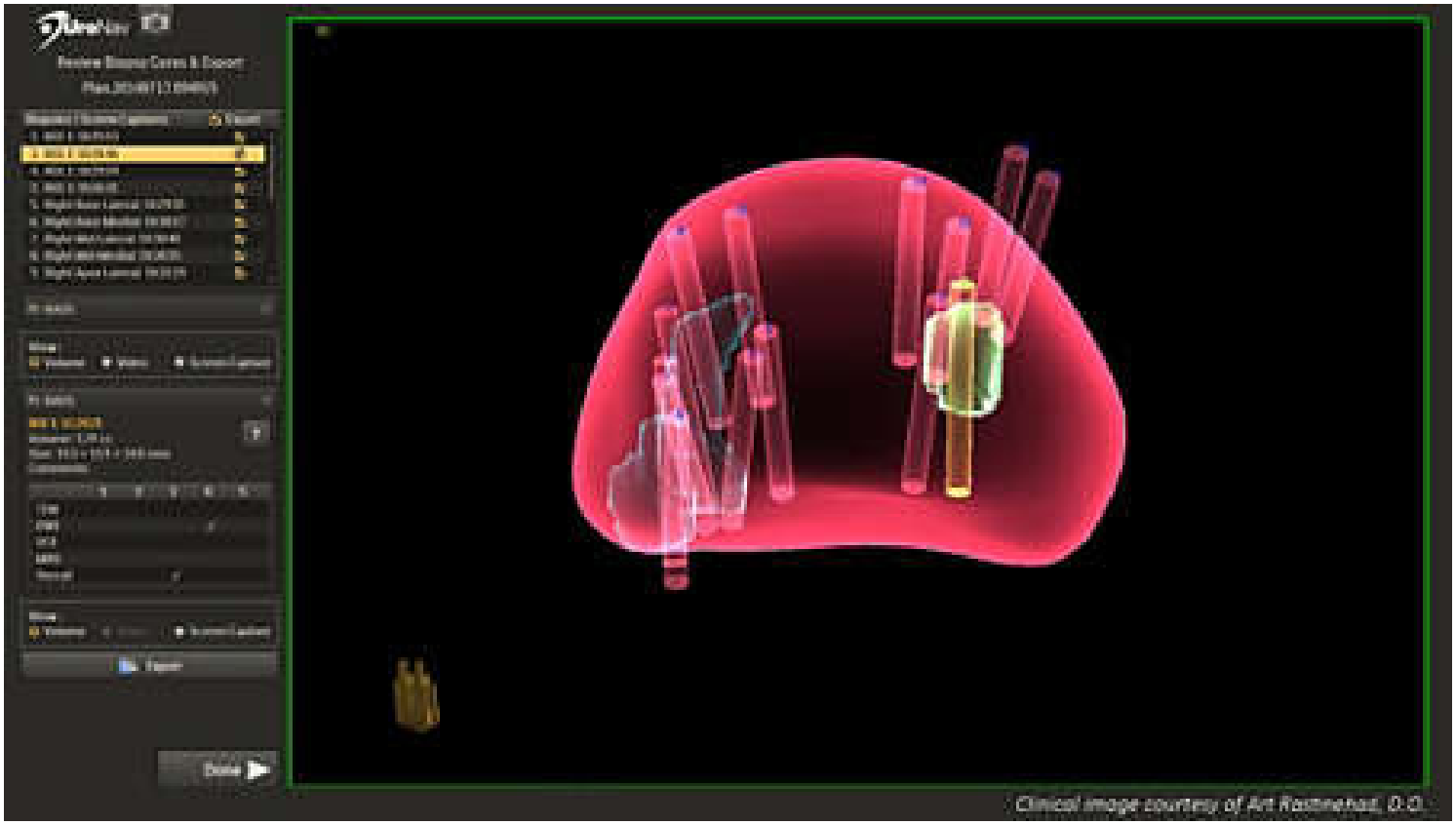


Most guideline groups recommend use of MRI before biopsy





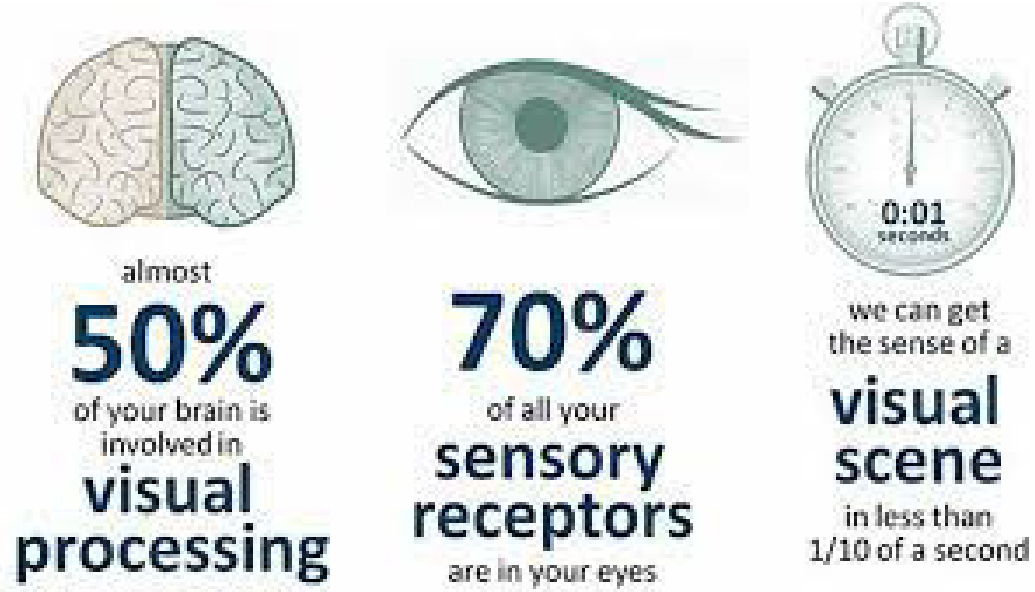
And the technology is simply stunning



But should you use it?

Well-known cognitive biases: precision

Cognitive bias: seeing is believing



We aren't going to talk about costs

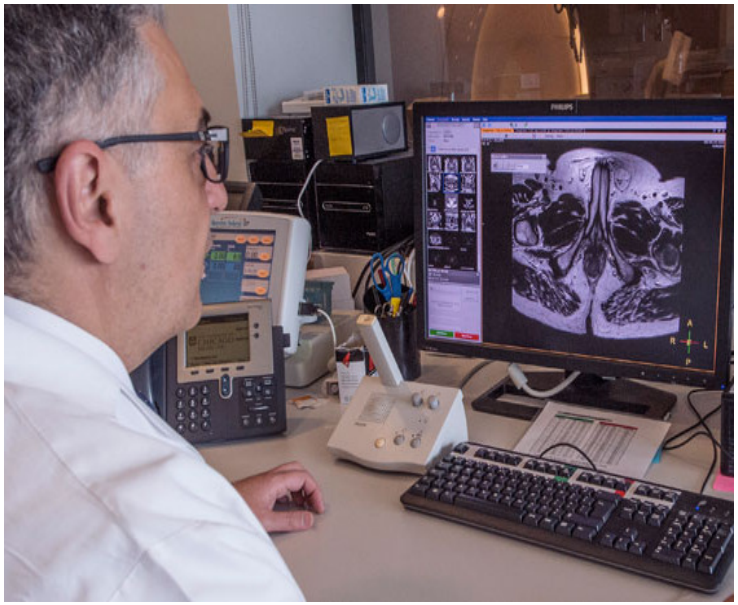
Viewpoint

December 2018

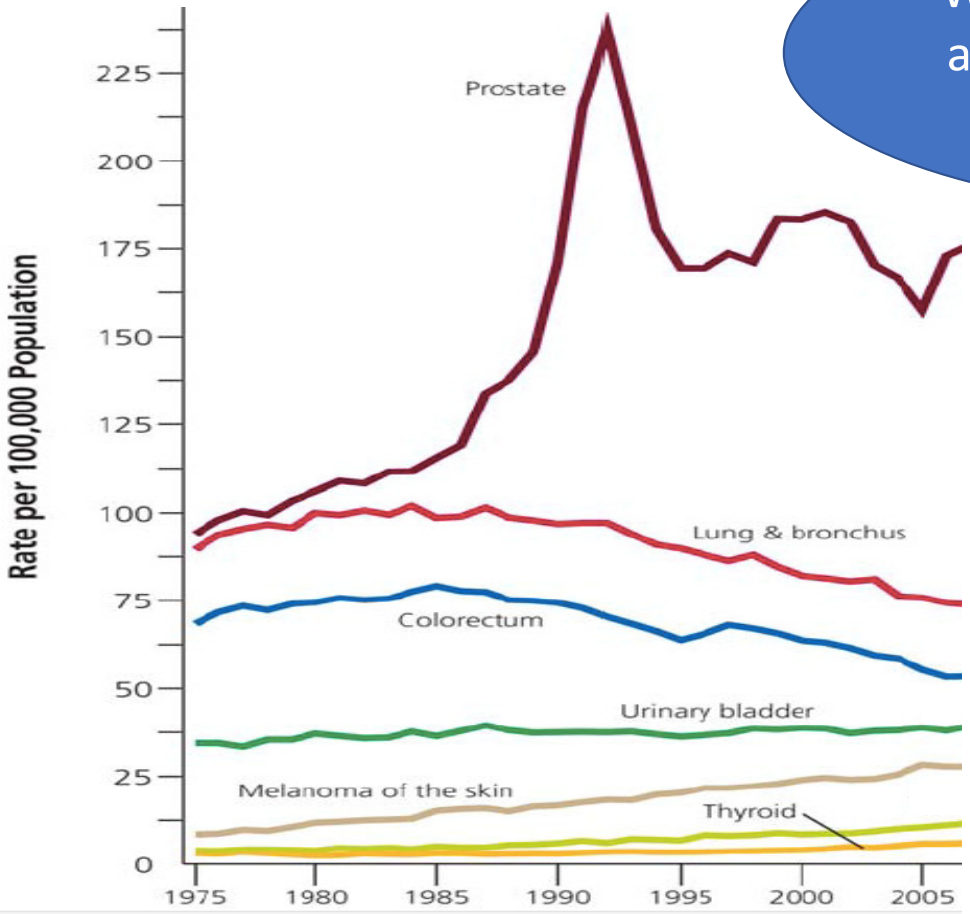
"… widespread mp-MRI adoption prior to biopsy would contribute $3 billion annually, that is, about 15% of the entire cost of managing prostate cancer would be related to a pre-diagnostic imaging test."

Two different roles for MRI in prostate cancer early detection

Specificity



Sensitivity



Wow! We really need to get a handle on underdiagnosis and undertreatment!

Outline of talk

- Mechanisms of overdiagnosis and overtreatment due to MRI-targeting
- Empirical evidence on MRI-targeting overdiagnosis and overtreatment
- The way forward

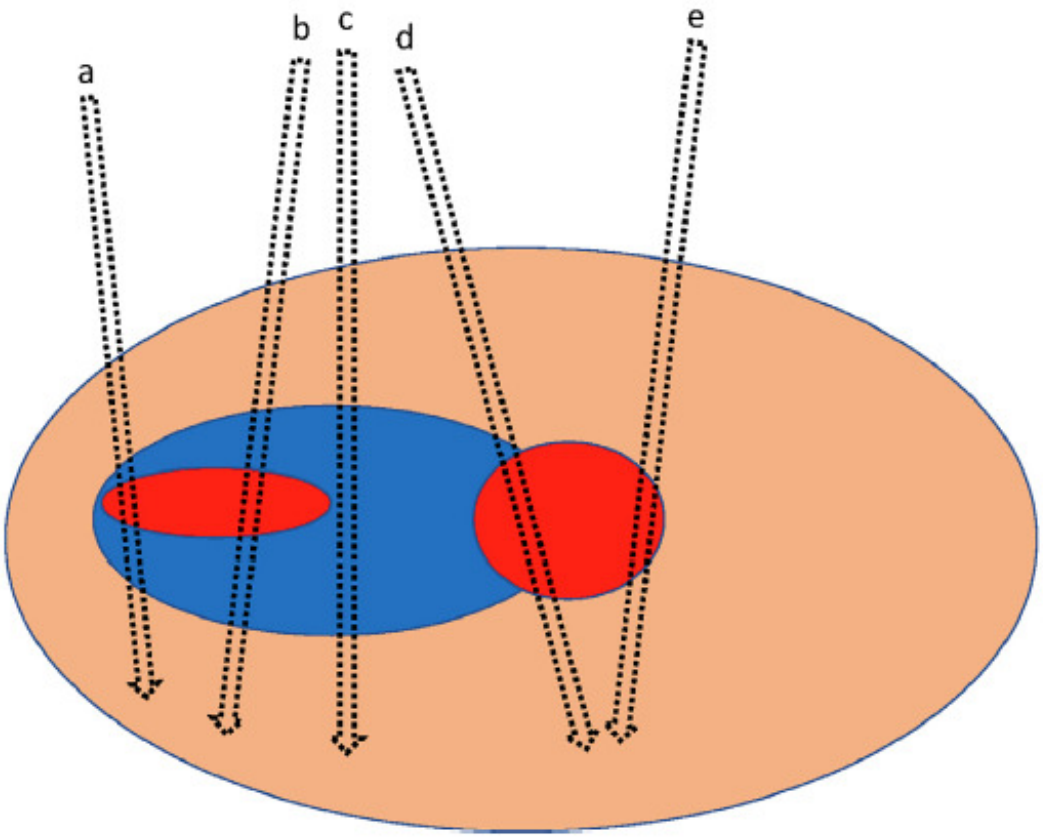
Outline (in brief)

- Gleason grade is a surrogate outcome

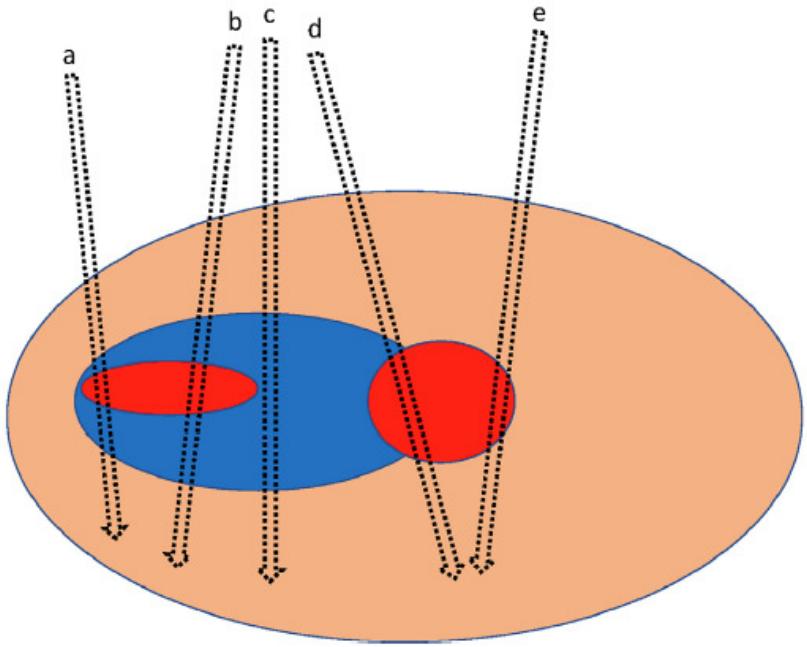
Outline of talk

- Mechanisms of MRI overdiagnosis and overtreatment
- Empirical evidence on MRI overdiagnosis and overtreatment
- The way forward

Grade isn’t an inherent property of a tumor



Rule of “highest grade counts” leads to higher grading for MRI targeted



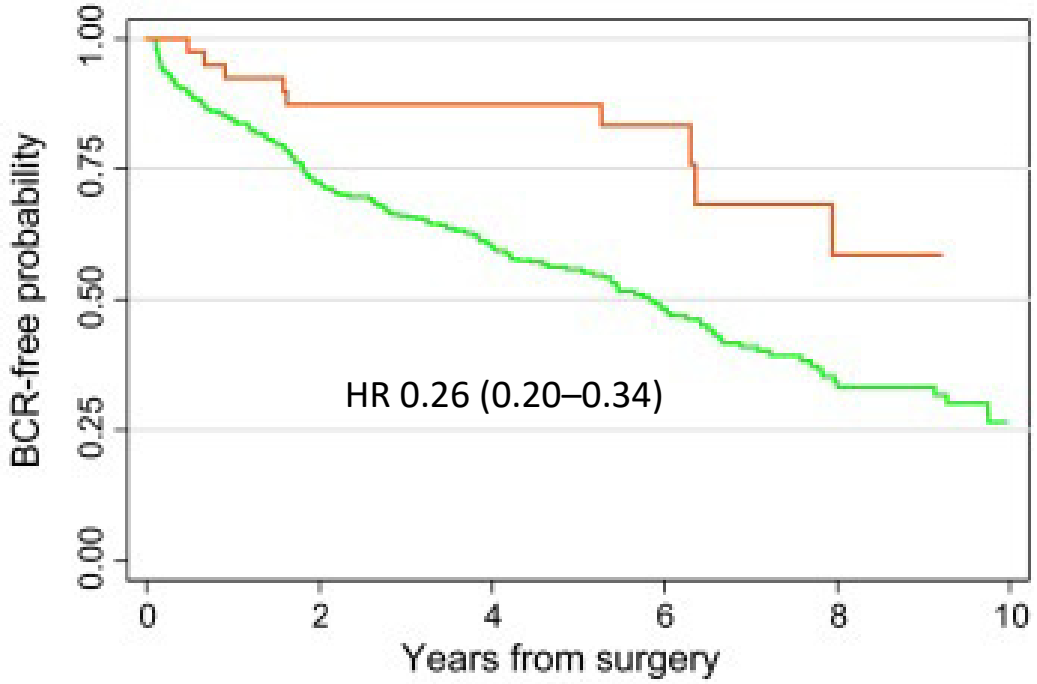
Type of biopsy	3+3	3+4	4+3	4+4
Systematic	20%	40%	20%	20%
Targeting: 3 cores	0%	10%	30%	60%
Targeting: 4 cores	0%	0%	20%	80%

If you can’t find the car keys, they are still there

Risk depend on method of detection

Thank god we removed your Gleason 6 prostate. It was really a Gleason 7

BCR risk for high-grade (4+3) on surgical pathology is dramatically reduced for clinical low-risk



Number at risk						
Low	41	34	31	13	5	2
Int/High	432	301	211	85	32	14

Mortality risk for high-grade (4+3) on surgical pathology is dramatically reduced for clinical low-risk

BJUI
BJU International

Effects of pathological upstaging or upgrading on metastasis and cancer-specific mortality in men with clinical low-risk prostate cancer

Evan Kovac*, Emily A. Vertosick†, Daniel D. Sjoberg†, Andrew J. Vickers† and Andrew J. Stephenson*

*Glickman Urological and Kidney Institute, Cleveland Clinic Foundation, Cleveland, OH, and †Department of Epidemiology and Biostatistics, Memorial Sloan Kettering Cancer Center, New York, NY, USA

Objectives

To determine if the presence of adverse pathological features in patients eligible for active surveillance (AS) are prognostic of

with adverse pathological features were significantly lower in those with low clinical risk, with an ~50% and ~70% reduction in the risk of metastasis and death, respectively. Only pathological upgrading/upstaging to Gleason score ≥8,

Risk of death for high-grade on surgical pathology is dramatically reduced for clinical low-risk

BJUI
BJU International

Of ~1000 low risk patients, cancer-specific mortality at 10 years

50% upgraded to 3+4: 0%

7% upgraded to 4+3: 0%

3% upgraded to 4+4: 6%

Hazard ratio for death surgery Gleason 7+: 0.19 if clinical low-risk

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- Empirical evidence on MRI overdiagnosis and overtreatment
- The way forward

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*

ABSTRACT

BACKGROUND

Multiparametric magnetic resonance imaging (MRI), with or without targeted biopsy, is an alternative to standard transrectal ultrasonography–guided biopsy for

The authors' full names, academic degrees, and affiliations are listed in the Ap-

PRECISION results

Outcome	MRI-Targeted Biopsy Group (N = 252)	Standard-Biopsy Group (N = 248)
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)

Fewer low-grade cancers! Exactly what the doctor ordered!

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More high-grade cancers! Thank god we found them!

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Same number of cancers overall. Err.....

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TOTAL:	118	119

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

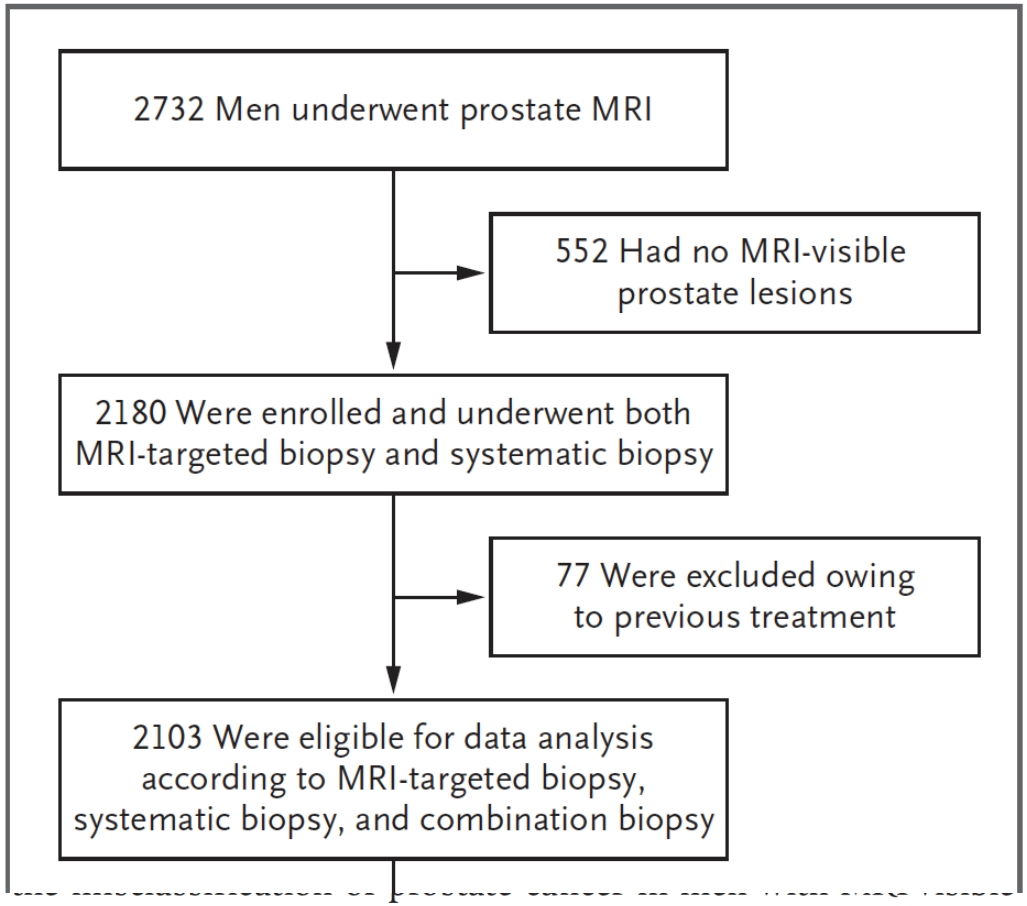
ABSTRACT

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

Men with MRI-visible prostate lesions underwent both MRI-targeted and systematic



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METHODS

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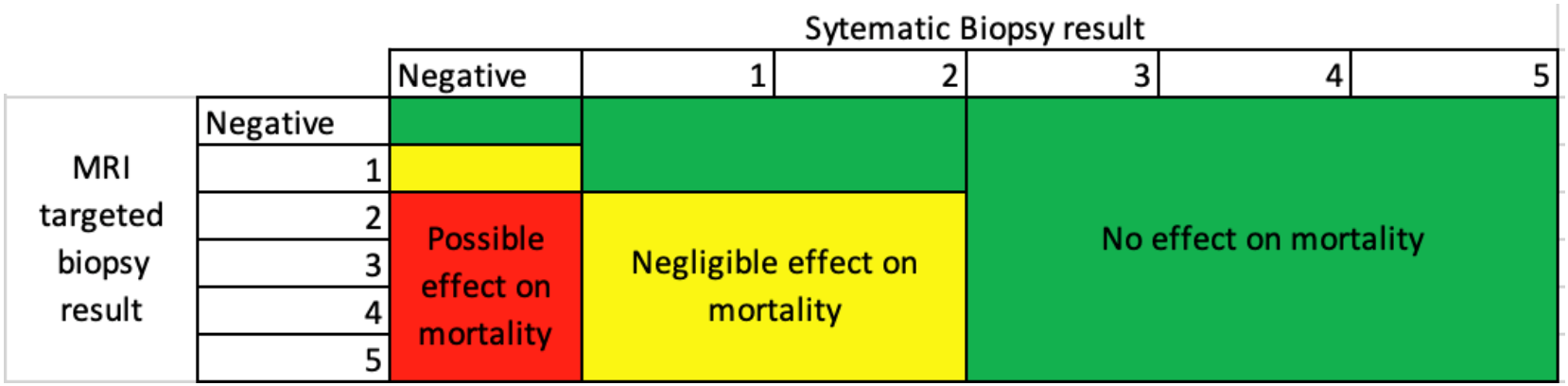
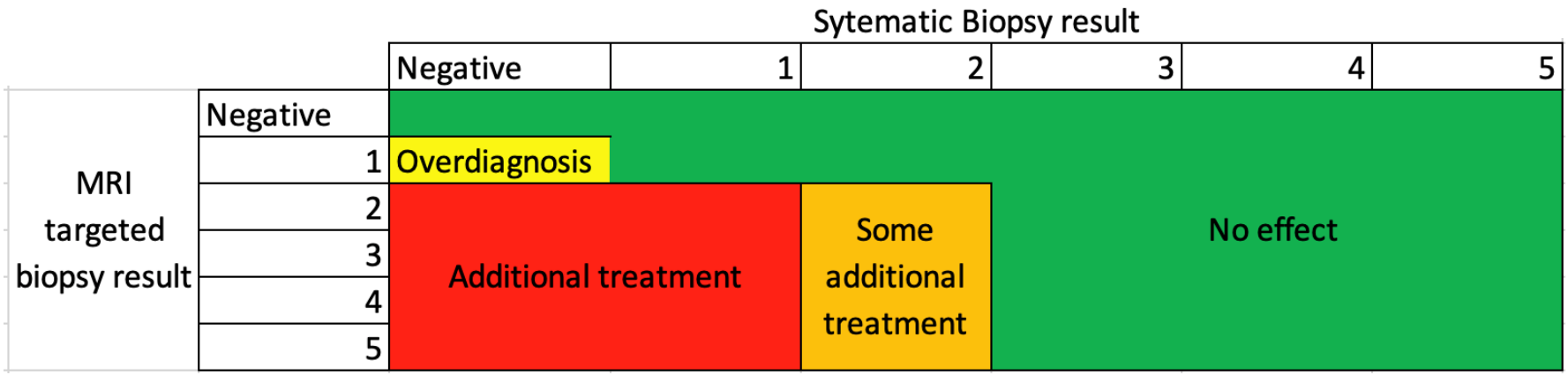
We do targeted-MRI to prevent prostate cancer death



But targeted MRI biopsy may increase treatments and diagnoses



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

reduce the misclassification of prostate cancer in men with MRI-visible lesions.

METHODS

Men with MRI-visible prostate lesions underwent both MRI-targeted and systematic

The NEW INE

Systematic Biopsy

MRI Biopsy

	No cancer	1
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BACKGR
The us tic inac-
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METHO
Men with MRI-visible prostate lesions underwent both MRI-targeted and systematic

The NEW ENGLAND JOURNAL of MEDICINE

MRI targeting: more cancers found, more men treated

ORIGINAL ARTICLE

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

- 999 men with negative systematic biopsy
  - 208 (21%) with cancer on MRI
  - 134 (13%) with high-grade disease
- 454 with grade group 1 on systematic biopsy
  - 134 (30%) with high-grade on MRI

cancer. Biopsies performed with magnetic resonance imaging (MRI) targeting may reduce the misclassification of prostate cancer in men with MRI-visible lesions.

METHODS

Men with MRI-visible prostate lesions underwent both MRI-targeted and systematic

We don’t need to find high-grade cancer in men with low-grade on systematic

Long-Term Outcomes of Active Surveillance for Prostate Cancer: The Memorial Sloan Kettering Cancer Center Experience

Sigrid Carlsson,* Nicole Benfante, Ricardo Alvim, Daniel D. Sjoberg, Andrew Vickers,† Victor E. Reuter, Samson W. Fine, Hebert Alberto Vargas, Michal Wiseman, Maha Mamoor, Behfar Ehdaie, Vincent Laudone, Peter Scardino, James Eastham and Karim Touijer‡

From the Urology Service, Department of Surgery (SC, NB, RA, MW, MM, BE, VL, PS, JE, KT), Department of Epidemiology and Biostatistics (SC, DDS, AV), Department of Pathology (VER, SWF) and Department of Radiology (HAV), Memorial Sloan Kettering Cancer Center, New York, New York, and Institute of Clinical Sciences, Department of Urology, Sahlgrenska Academy at the University of Gothenburg, Gothenburg, Sweden (SC)

Abbreviations and Acronyms

ADT = androgen deprivation therapy

AS = active surveillance

MRI = magnetic resonance imaging

PSA = prostate specific antigen

RP = radical prostatectomy

Accepted for publication December 13, 2019.

Presented at annual meeting of the American Urological Association, San Francisco, California, May 19, 2018.

Supported by the Sidney Kimmel Center for Prostate and Urologic Cancers, a Specialized Programs of Research Excellence grant (P50 CA92629) from the National Cancer Institute, a National Institutes of Health/National Cancer Institute Cancer Center Support Grant (P30 CA008748) to Memorial Sloan Kettering Cancer Center and the David H. Koch prostate cancer

Purpose: We report oncologic outcomes for men with Grade Group 1 prostate cancer managed with active surveillance at a tertiary cancer center.

Materials and Methods: A total of 2,907 patients were managed with active surveillance between 2000 and 2017, of whom 2,664 had Grade Group 1 disease. Patients were recommended confirmatory biopsy to verify eligibility and were followed semiannually with prostate specific antigen, digital rectal examination and review of symptoms. Magnetic resonance imaging was increasingly used in recent years. Biopsy was repeated every 2 to 3 years or after a sustained prostate specific antigen increase or changes in magnetic resonance imaging/digital rectal examination. The Kaplan-Meier method was used to estimate probabilities of treatment, progression and development of metastasis.

Results: Median patient age at diagnosis was 62 years. For men with Grade Group 1 prostate cancer the treatment-free probability at 5, 10 and 15 years was 76% (95% CI 74–78), 64% (95% CI 61–68) and 58% (95% CI 51–64), respectively. At 5, 10 and 15 years there were 1,146, 220 and 25 men at risk for metastasis, respectively. Median followup for those without metastasis was 4.3 years (95% CI 2.3–6.9). Distant metastasis developed in 5 men. Upon case note review only 2 of these men were deemed to have disease that could have been cured on immediate treatment. The risk of distant metastasis was 0.6% (95% CI 0.2–2.0) at 10 years.

We don’t need to find high-grade cancer in men with low-grade on systematic

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From
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2,907 men

5 cases of metastasis

2 potentially preventable

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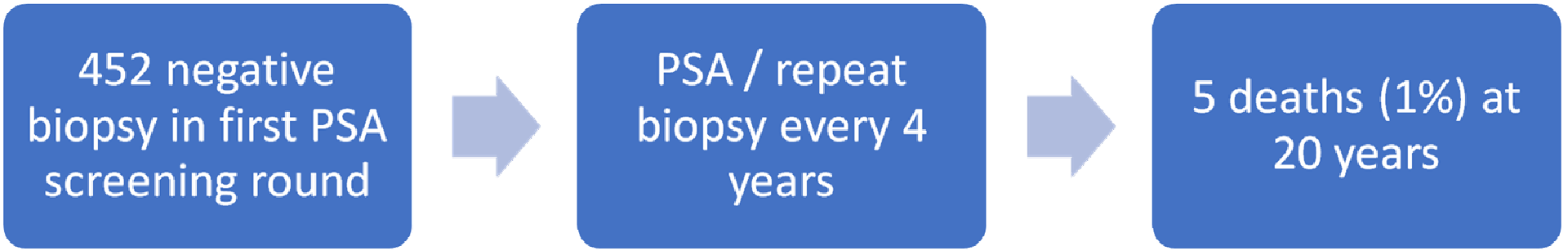
Almost zero long-term risk of mortality in men with negative *sextant* biopsy if PSA < 10 ng / ml

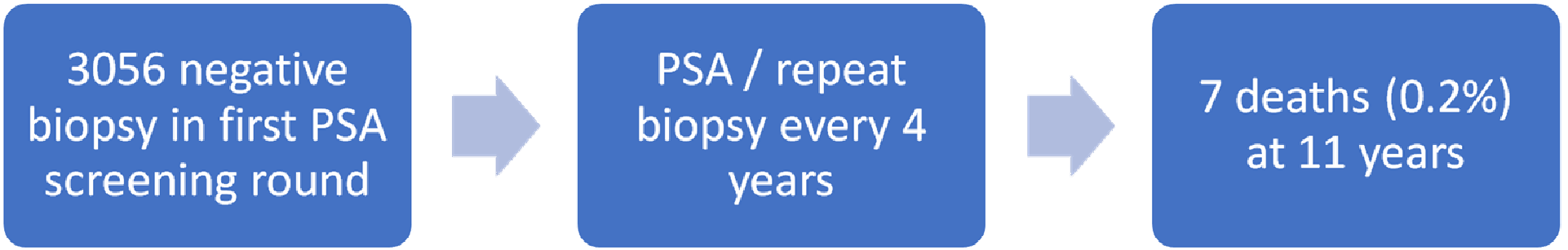
ERSPC Goteborg confirms very low risk of death in patients with negative sextant



Likely zero deaths in 452 negative biopsies Goteborg under contemporary practice

Patient	PSA at bBx (ng/ml)	Time from bBx to PC Dx (yr)	Age at PC Dx (yr)	Time from Dx to PC death (yr)
1	5.2	8.8	72.7	3.7
2	73.1	1.9	65.5	12.8
3	12.5	8.3	66.0	8.9
4	3.7	10.1	75.2	5.3
5	33.5	1.0	62.5	13.8

ERSPC Rotterdam confirms very low risk of death in patients with negative sextant



Compare ERSPC vs. NCI

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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

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

Article info

Article history:
Accepted October 27, 2009
Published online ahead of print on November 6, 2009

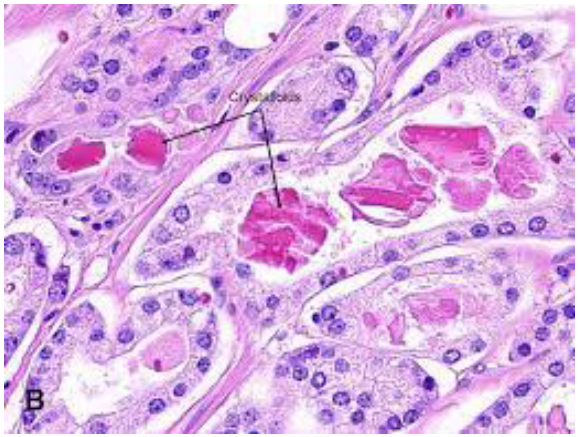
Keywords:
Prostate cancer

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

Compare ERSPC vs. NCI

Diagnoses in NCI



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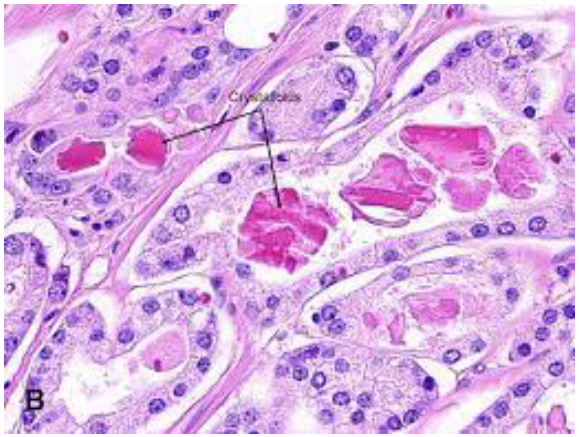
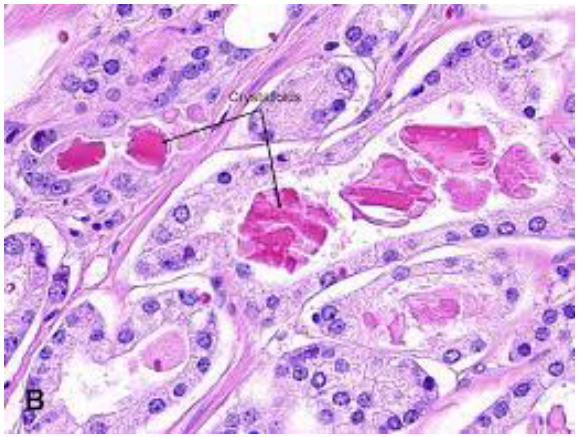
Diagnoses in NCI



Deaths in ERSPC

Compare ERSPC vs. NCI

Diagnoses in NCI



Deaths in ERSPC

How many cancers per death averted?

Modeling study requires assumptions

Number	Description
1	Patients with Grade Group 1 disease are managed conservatively whereas those with Grade Group 2 or higher receive curative therapy. No patients on conservative management crossover to treatment.
2	The grade distribution of cancers identified during follow-up in the ERSPC study is similar to that of the MRI-detected cancers in patients in the NCI study who had no cancer on TRUS biopsy.
3	MRI would have detected 75% of the tumors subsequently diagnosed in later rounds of the ERSPC.
4	Of the men with negative systematic biopsy who died in the ERSPC study, MRI-targeting would have detected 90% of the tumors.
5	Immediate treatment of patients with cancers detected on MRI-targeting reduces the risk of prostate cancer death by 75%.
6	Any benefits from MRI in avoiding repeat biopsy are approximately equivalent to MRI-induced harms of additional years with treatment-related morbidity related to earlier diagnosis and treatment.

MRI-targeting leads to excessive overdiagnosis and overtreatment

Scenario	NND	NNT
Base case with favorable assumptions for MRI	**89.1**	**57.0**
Neutral assumptions for properties of MRI and effects of treatment	**169.1**	**126.9**
Extreme case of maximally perfect properties of MRI and treatment	**49.9**	**24.9**
Neutral assumptions for properties of MRI, conservative assumptions for effects of treatment	338.3	253.7
Dramatic reduction in treatment rates but same cure rates	89.1	31.2
12-core biopsy finds more disease, but no fatal cancer	80.0	51.5
12-core biopsy finds more disease, including some fatal cancer	96.0	61.8
Some deaths avoided by clinical use of MRI in men with negative biopsy and high PSA	118.8	76.5

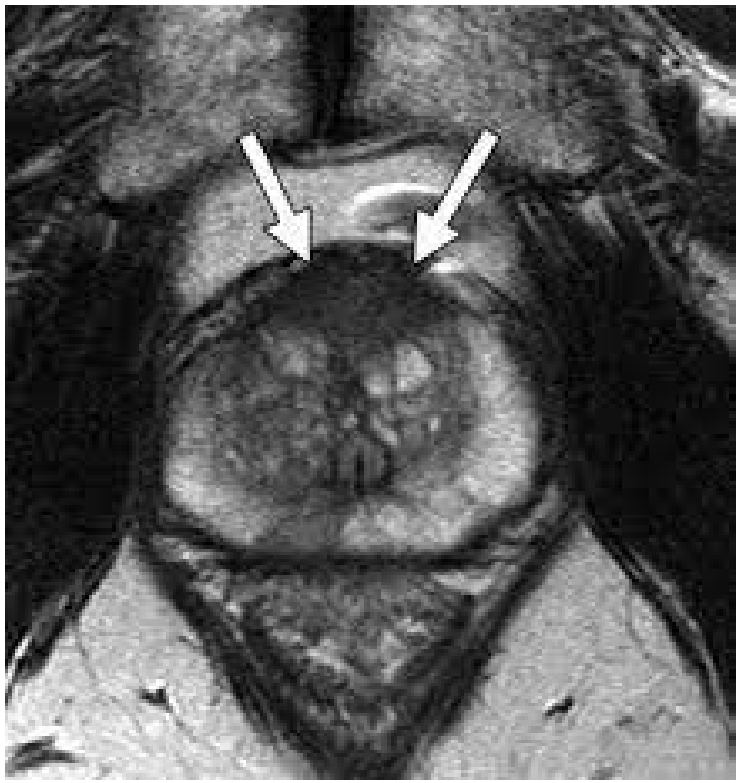
Outline of talk

- Mechanisms of MRI overdiagnosis and overtreatment
- Empirical evidence on MRI overdiagnosis and overtreatment
- The way forward

MRI is not going away

Clear clinical indication for MRI

- Negative biopsy at PSA of 8 ng/mL
- PSA two years later of 17.2 ng/mL



Current guidelines call for treatment irrespective of method of detection

National Comprehensive Cancer Network®

NCCN Guidelines Version 4.2019
Prostate Cancer

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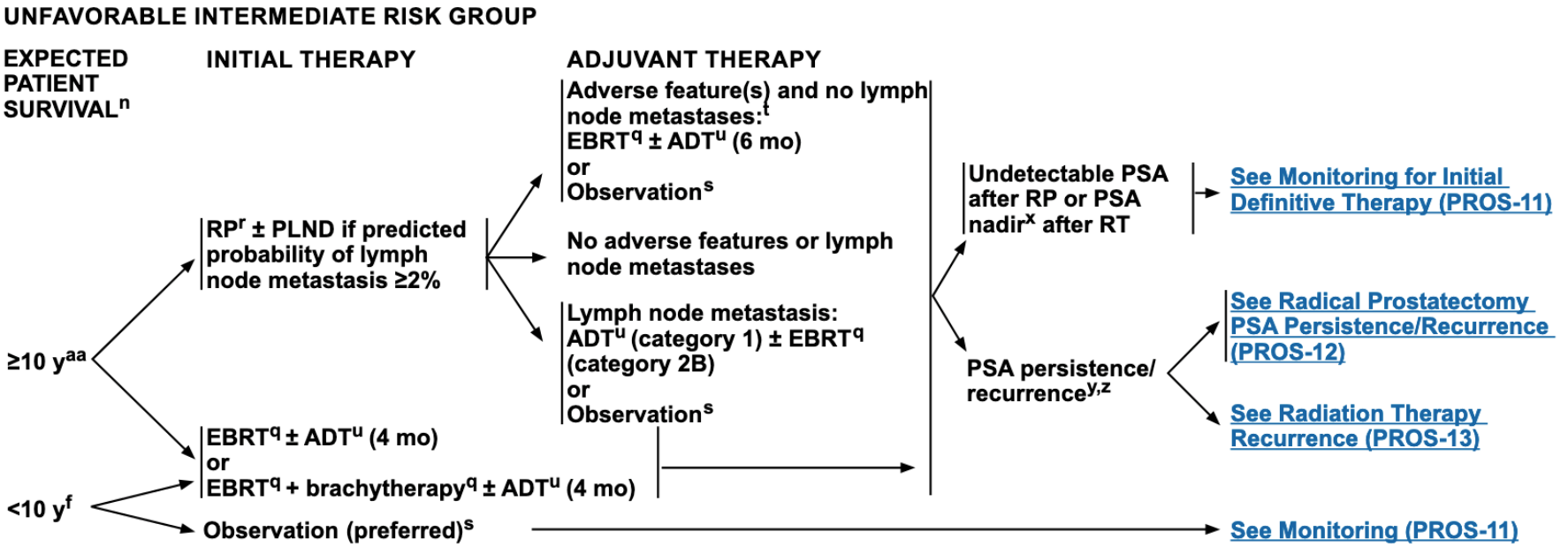

Christopher J. Kane @cjkane10 · May 20, 2020

Replying to @VickersBiostats

Agree with Eric Klein the component of G4 is present, likely significant, will probably be p3+4 but I'd treat

1

Eduardo GL @edugloarte · May 19, 2020

Agree with Dani. My opinion is that nowadays there are no reason for managing an active surveillance program without mp-MRI. We were blind for a lot of time. Now we can see.
ISUP grade 3. Very very risky the AS!

1 2

Rafael Sanchez-Salas @RSanchez_Salas · May 21, 2020

Replying to @VickersBiostats

Active treatment due to 4+3. Depending on patient's expectation, prostate size, biopsies - MRI images concordance and prostate volume a focal therapy trial option could be discussed.

Ricardo Soares @soares_uro · May 19, 2020

Replying to @VickersBiostats

In my mind that is a Gleason 3+4, the most likely grade on RP specimen. You need to consider PSA, PSA density, size and location of MRI lesion. And then discuss with the patient.

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Andrew Vickers
@VickersBiostats

Question for urologists and esp. MRI advocates. A patient has combined systematic / targeted biopsy. Systematic shows 1 core 3+3. Targeted is 3 cores: 1 3+3, 1 4+3, 1 benign. Patient would be active surveillance on systematic but is 4+3 due to MRI. Recommendation?

Conclusions

- MRI-targeting finds more high-grade cancers
  - These lead to treatment
  - Evidence is that these are low risk
- MRI-targeting plus contemporary treatment guidelines leads to:
  - **Considerable overdiagnosis and overtreatment**
- Recommendations
  - More restrictive use of MRI-targeting
  - Change treatment guidelines for MRI detected tumors
  - Research on oncologic risk of MRI-detected tumors