Active surveillance

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Outline

- Rationale for active surveillance
- Trends in active surveillance utilization
- Barriers to uptake of active surveillance
- Protocols for selection and monitoring

Screening Controversy

- 2012 USPSTF Grade D recommendation
  - Per 1000 men screened:
    - 1 fewer prostate cancer death
    - 30-40 men with incontinence or erectile dysfunction due to treatment
    - 2 men with serious cardiovascular events
    - 1 venous thrombosis
- 2014 Canadian Task Force on Preventive Health Care (CTFPHC) recommended against PSA

www.uspreventativeservicestaskforce.org
http://canadiantaskforce.ca/ctfphc-guidelines/2014-prostate-cancer/

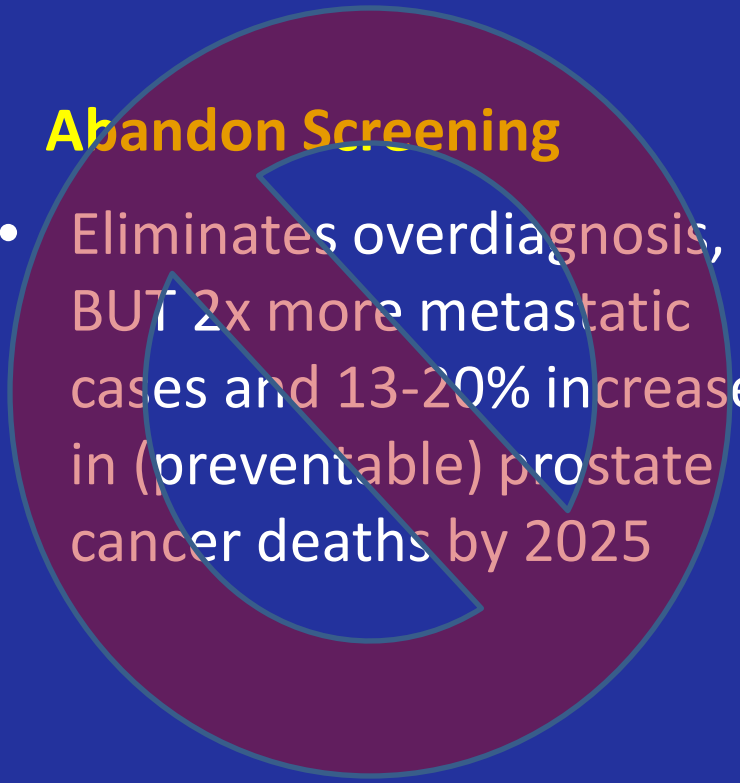
Overdiagnosis and Overtreatment of Prostate Cancer

Stacy Loeb[a,*], *Marc A. Bjurlin*[a], *Joseph Nicholson*[b], *Teuvo L. Tammela*[c], *David F. Penson*[d], *H. Ballentine Carter*[e], *Peter Carroll*[f], *Ruth Etzioni*[g]

- Up to 67% cases overdiagnosed depending on the population and criteria

- Historically the vast majority of low-risk patients received radical treatment
  - Overtreatment → unnecessary side effects

How to Reduce Harms



Abandon Screening

- Eliminates overdiagnosis, BUT 2x more metastatic cases and 13-20% increase in (preventable) prostate cancer deaths by 2025

Reduce Overdiagnosis & Overtreatment

- Better patient selection for screening
- Better screening and biopsy paradigms
  - Use of markers and imaging
  - Targeted biopsy
- **Better patient selection for treatment**
  - **Increase uptake and durability of active surveillance**
- Better treatment

Gulati et al. Cancer 2014; 120: 3519.

Reviews

BJUI
BJU International

The Melbourne Consensus Statement on the early detection of prostate cancer

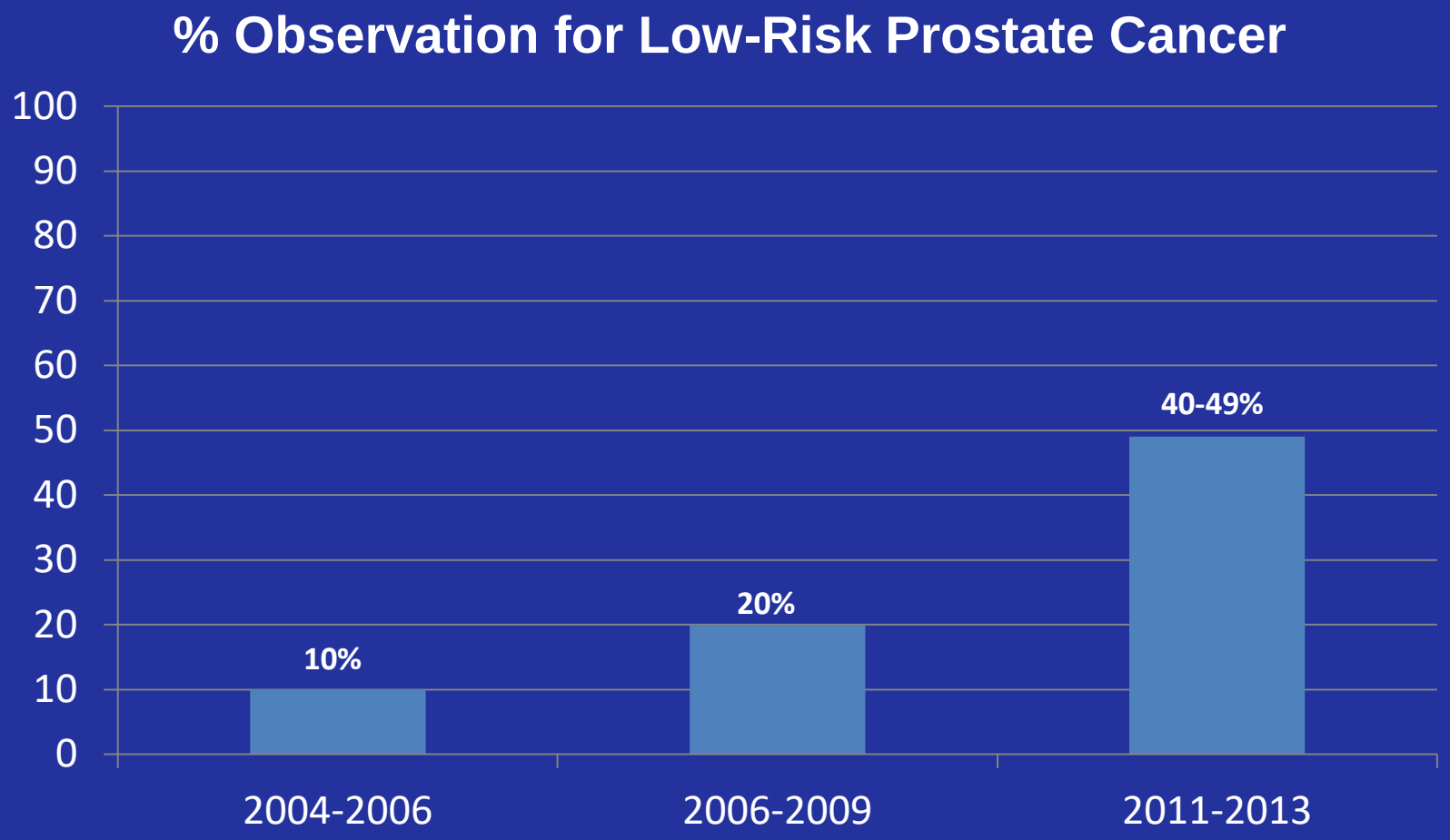
Declan G. Murphy[1,2,3], Thomas Ahlering[4], William J. Catalona[5], Helen Crowe[2,3], Jane Crowe[3], Noel Clarke[10], Matthew Cooperberg[6], David Gillatt[11], Martin Gleave[12], Stacy Loeb[7], Monique Roobol[14], Oliver Sartor[8], Tom Pickles[13], Addie Wootten[3], Patrick C. Walsh[9] and Anthony J. Costello[2,3]

- Consensus Statement 2: “Prostate cancer diagnosis must be uncoupled from prostate cancer intervention”

- “Further developments in the area of biomarkers, as well as improvements in imaging will continue to improve risk stratification, with potential for reduction in over-diagnosis and over-treatment of lower risk disease”

Are we making progress?

Reducing Overtreatment in USA



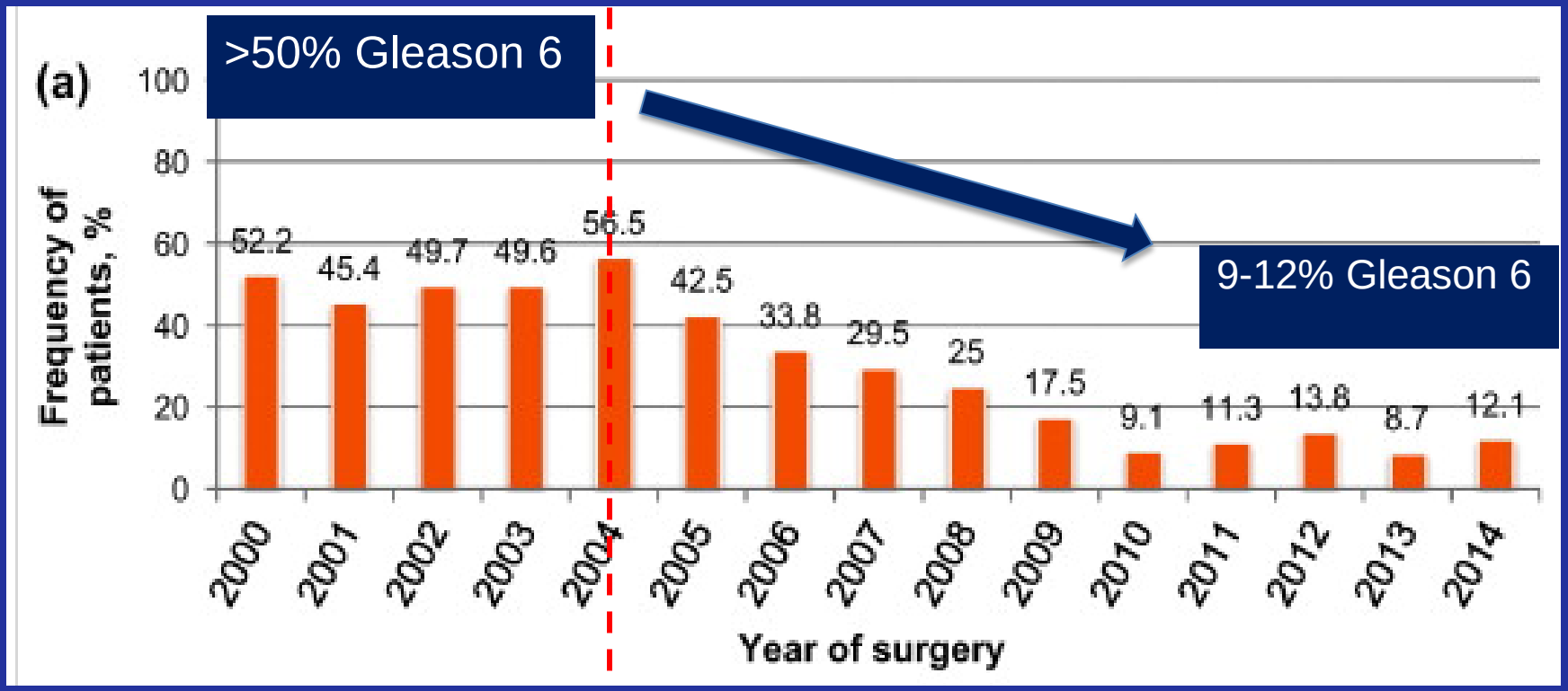
Cooperberg 2007, Hoffmann 2014, Ingimarsson et al. CCC 2015, Womble et al. Eur Urol 2014, Cooperberg et al. JAMA 2015

Brief Correspondence

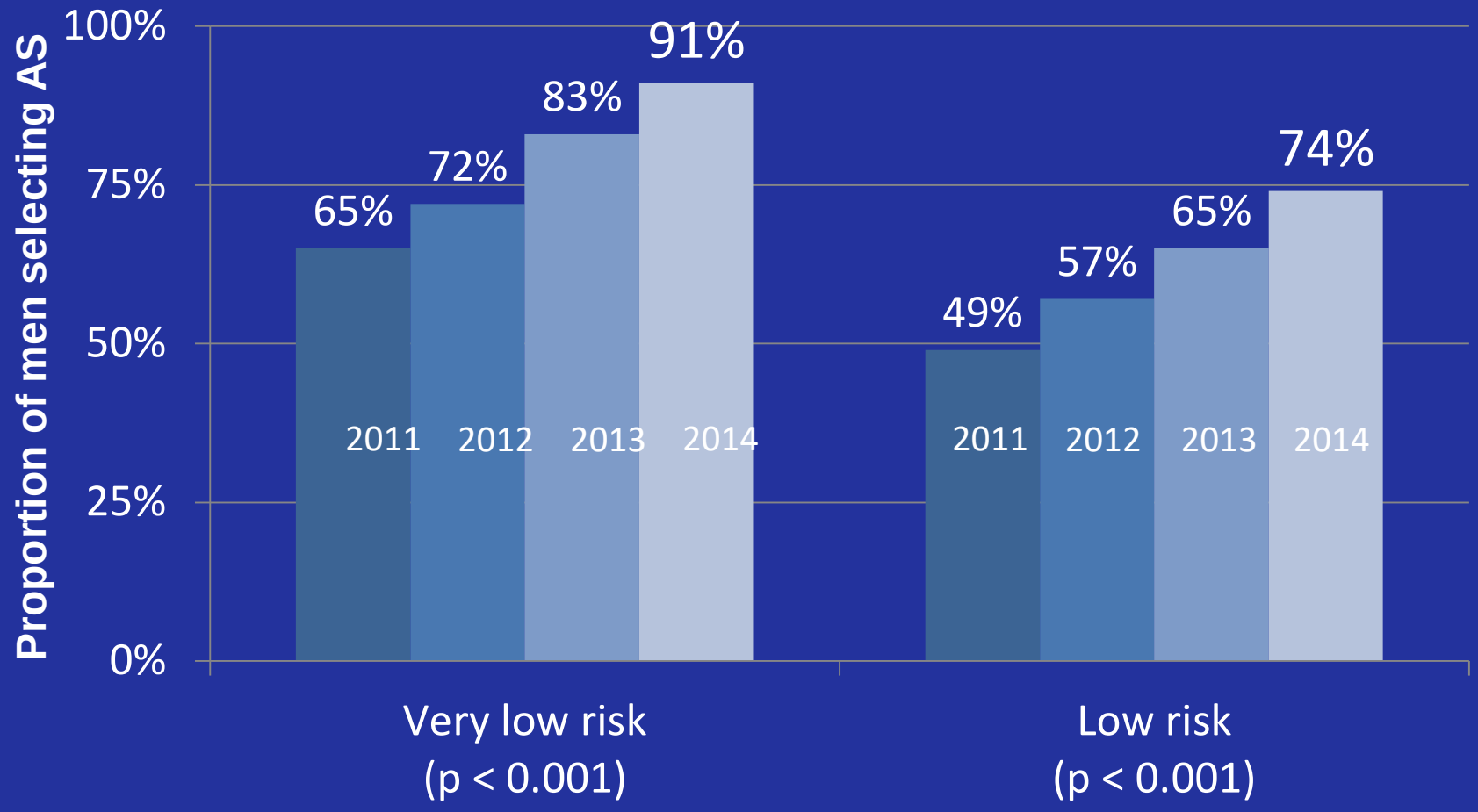
Changing Trends in Surgical Management of Prostate Cancer: The End of Overtreatment?

Hartwig Huland, Markus Graefen *

Martini-Clinic Prostate Cancer Center, University Hospital Hamburg-Eppendorf, Hamburg, Germany



New Swedish Nationwide Data (2011-2014)



Loeb et el. JAMA Oncology 2016 in press

Increasing Use of AS Among Young Men

Very Low Risk

Age	2009	2014
<55	44%	84%
55-60	45%	90%
60-64	60%	92%

Low Risk

Age	2009	2014
<55	22%	59%
55-60	33%	71%
60-64	40%	74%

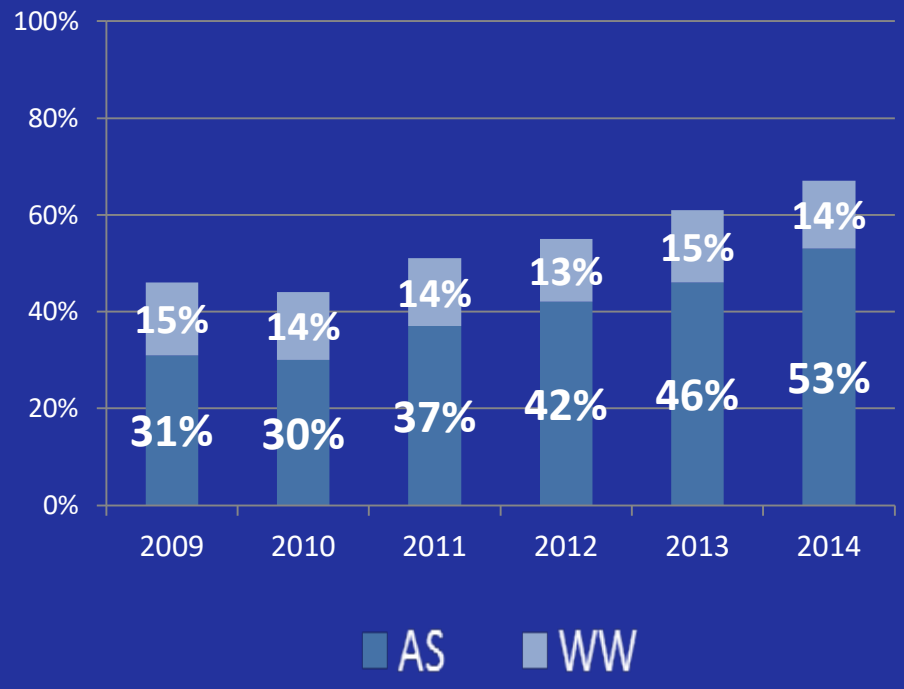
Loeb et al. AUA 2016

AS for Intermediate Risk Disease

Loeb et el. JAMA Oncology 2016 in press

Higher Use for Intermediate-Risk Based on PSA Only vs. Gleason

Gleason 6, PSA 10-20



Gleason 3+4, PSA <10

Loeb et el. JAMA Oncology 2016 in press

Medscape Medical News > Conference News

'Era of Active Surveillance Has Arrived' in Prostate Cancer

Nick Mulcahy

May 16, 2015

7 comments Print

JOURNAL OF CLINICAL ONCOLOGY | ASCO SPECIAL ARTICLE

Active Surveillance for the Management of Localized Prostate Cancer (Cancer Care Ontario Guideline): American Society of Clinical Oncology Clinical Practice Guideline Endorsement

- Recommended management for most low-risk patients (Gleason ≤6)
- May be offered to select patients with low-volume, intermediate-risk PCa (Gleason 3+4=7)
- Watchful waiting more appropriate if <5 year life expectancy

Chen et al. JCO 2016 epub.

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Increasing Patient Acceptance of AS- Renaming "Gleason 6" Disease

- "Cancer" is an emotion-laden term but Gleason 6 has limited metastatic potential
  - Proposals to remove "cancer" label- NOT adopted
- New grade groups adopted reclassifying 6-10 as 1-5

Traditional Gleason score	Grade group
6	1
3+4=7	2
4+3=7	3
8	4
9-10	5

Epstein et al. Eur Urol 2016 epub

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

European Association of Urology

Research Letter

Perspectives of Prostate Cancer Patients on Gleason Scores and the New Grade Groups: Initial Qualitative Study

Stacy Loeb [a,b,c,*], *Caitlin Curnyn* [b], *Erica Sedlander* [b]

- 80% of patients feel more comfortable with active surveillance for “grade group 1” vs “Gleason 6”

Increasing Acceptance of AS-
Qualitative data on Challenges for US Providers

- **Varying experience/exposure to AS during training**
  - *"We train people to do something. We are by nature doers and AS is not really part of what a surgeon is wired to do."*
- **Concerns about inflicting "harm" and legal risk**
  - *"It's possible that you miss the window of curability on your watch. They could be hurt by that choice. That's a lot of responsibility."*
  - *"There's obviously some degree of liability."*
- **Financial incentives**
  - *"In Europe where there is no fee for service system the uptake of AS is exponentially higher than it is in the U.S."*

Loeb et al. BJUI 2016 epub.

Prostate Cancer Advertising

"The country's most experienced prostate cancer cyberknife team"

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Eligibility for Active Surveillance

- PSA <10 or <15 ng/ml
  - Optional: PSA density (PSA/prostate volume): <0.15 or <0.2
- Clinical Stage T1 (nonpalpable) ± T2 (palpable)
- Biopsy features
  - Gleason score: ≤6 ± 3+4=7
  - Extent of disease
    - <2-3 positive cores total (or ≤33-50% of all cores positive)
    - 20-50% maximal cancerous involvement of any core

Tosoian et al. Nat Rev Urol 2016; 13: 205.

Improving Patient Selection

- PSA, clinical stage and standard biopsy result in substantial rates of misclassification (>1/3)
- Substantial biologic heterogeneity within broad risk groups
- Role for imaging and biomarkers to refine selection

Shapiro & Johnstone Urology 2012; 80: 661. Loeb et al. Eur Urol 2013 epub. Lee et al. Can J Urol 2010; 17: 5429 Ross et al. JCO 2010; 28: 2810

Magnetic Resonance Imaging in AS

- Evidence synthesis: reclassification in 17% with negative MRI, 39% with positive MRI undergoing standard biopsy and 47% with MRI-targeted biopsy

- Substantial evidence that MRI is useful to confirm eligibility
  - UK National Institute for Health and Care Excellence (NICE) currently recommends performing MRI at AS initiation

Schoots et al. Eur Urol 2015; 67: 627

Tissue Tests for Risk Stratification

	Company	Reported Endpoint
Prolaris	Myriad	Prostate cancer death
OncotypeDX	Genomic Health	Adverse pathology at prostatectomy
Decipher	GenomeDx	High Grade Disease Metastasis Prostate cancer death

AS Monitoring is Heterogeneous

- PSA every 3-6 months
- Digital rectal examination every 6-12 months
- Repeat biopsy every 1-5 years
- Variable use of MRI and other markers

Loeb et al. Rev Urol 2014; 16: 22.

Current Challenges- Monitoring During AS

- Changes in PSA not reliable
  - AUC 0.59 for biopsy reclassification
- Biopsy-based AS presents significant risks and patient burden
  - ↑ infections over time due to antibiotic resistance
  - Other risks: bleeding, pain, LUTS, possible ED
  - Source of non-compliance

Ross et al. JCO 2010; 28: 2810. Loeb et al. J Urol 2011; 186: 1830.
Loeb et al. Eur Urol 2013; 64: 876.

Biopsies During AS (SEER-Medicare)

Tests received by 1349 men on AS for 5y	% of patients
PSA	
≥5 PSA (yearly)	91%
≥10 PSA (2x/yr)	59%
Biopsy	
≥2 biopsies	34%
≥3 biopsies	15%
Combination	
≥10 PSA + ≥2 biopsies	22%

Need for more data on serial MRI and additional non-invasive testing options

Loeb et al. J Urol 2016 epub.

Markers & Imaging During AS

- Prostate health index (phi): Blood test combining PSA, free PSA, and [-2]proPSA: *phi = **([-2]proPSA/free PSA) x √PSA***
  - FDA approved for prostate cancer screening
  - Longitudinal phi predicts progression on AS (C-index 0.82)

- Magnetic resonance imaging
  - More data needed on serial MRI during AS
  - 2016 NCCN: repeat biopsy if MRI suggests more aggressive disease (+ fusion biopsy improves detection of high-grade PCa)

Tosoian et al. J Urol 2012; 188: 1131.
Hirama et al. J Cancer Res Clin Oncol 2014; 140: 257.
Schoots et al. Eur Urol 2015; 67: 627

Summary

- Use of active surveillance is increasing in many countries
- New grade groups increase patient acceptance of AS
- More experience and training on AS may increase uptake by physicians, but challenges remain
- Traditional eligibility and monitoring protocols have significant limitations → will improve with greater integration of new markers and imaging