Active Surveillance in the management of localized prostate cancer

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Not all prostate cancer is the same!

PSA screening allows for the diagnosis of prostate cancer often when it's at a localized and curable stage.

However, PSA screening detects a significant volume of clinically insignificant disease, which may ultimately never harm the patient.

Urologist's challenge is to reduce the risks of screening and treatment.

Screening morbidity

- Screening morbidity
  - Prostate biopsy – hematuria, hematochezia, < 1 % risk of sepsis
- Treatment for localized prostate cancer has morbidity
  - Urinary incontinence
  - Erectile Dysfunction
  - Irritative voiding symptoms
- Not all prostate cancer is equal.
  - Clinically significant vs Non-clinically significant

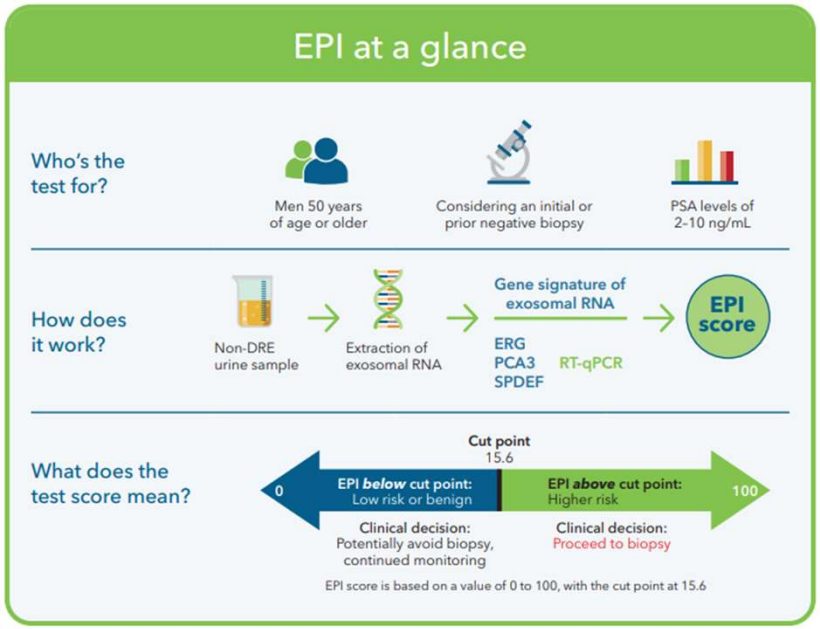
- Key is to screen in a way to avoid detecting low risk cancers while continuing to catch clinically significant disease.
- Reduces screening morbidity

How do we reduce unnecessary prostate biopsies? Beyond PSA…

- mpMRI
  - 80-90% NPV for clinically significant prostate cancer.
  - Depends on quality and training of radiologist
- PSA Density
  - PSA/prostate volume.
  - Cut point <0.1
    - low likelihood of clinically significant prostate cancer
- Biomarkers – urine and serum
  - pHI
  - 4KScore
  - ExoDx
  - MPS (My prostate Score)
  - Select MDX

ExoDx Prostate Intelliscore (EPI)

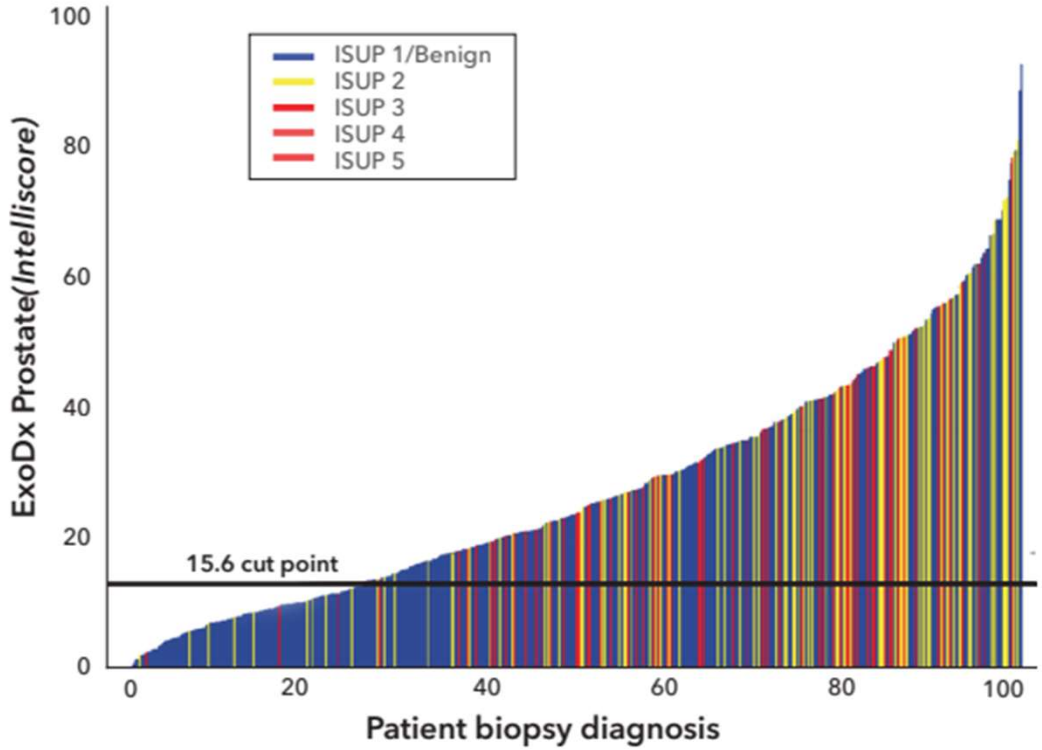
- Urine
- Age > 50
- PSA 2-10
- No DRE
- Risk of clinically significant prostate cancer : GG2 or greater
- RNA found in urine exosomes (vesicles secreted from cells)
- ETS transcription factor, ERG, PCA3
- Algorithm independent of PSA and clinical risk factors
- Score ranges from 0-100.
- At home collection kit



The 2019 NCCN guidelines include the ExoDx Prostate test (EPI) for early detection in men for both initial and prior negative biopsy.*

*The test was developed as a rule-out test (91.3% negative predictive value and 92% sensitivity in the initial biopsy cohort).

Figure 2: The EPI Test performed the same in two prospective validation studies published in top-tier peer-reviewed journals over 1,000 patients[4,5]



This chart represents >1,000 patients who were candidates for initial biopsy. All patients were in the intended use population (50 years of age or older, and PSA 2–10ng/mL).

Key Points:

- EPI was able to accurately classify patients that were not likely to need a biopsy (Gleason 6/GG1) with a score of 15.6 or less. Note the density of blue below the cut point (indicating ISUP1/benign)
- EPI was able to accurately classify patients that were more likely to need a biopsy (Gleason 7/GG2) with a score of 15.6. Note the high density of yellow and red color above the cut point, indicating Gleason 7 and above (indicating higher grade group and need for biopsy)
- ISUP 1/benign: Gleason 6
- ISUP 2: Gleason 7/(3+4)
- ISUP 3: Gleason 7/(4+3)

What is clinically insignificant prostate cancer?

NCCN Guidelines Prostate Cancer

- Very Low
  - Grade Group 1 (Gleason Score 6)
  - Non-palpable
  - PSA < 10 ng/ml
  - Fewer than 3 cores on prostate biopsy with all cores < 50 %
  - PSA density < 0.15 (PSAD= PSA/prostate volume)
- Low
  - Grade Group 1
  - T1-T2a (nodule involving <1/2 of one lobe of prostate on exam)
  - PSA < 10

What is clinically insignificant prostate cancer

NCCN Guidelines Prostate Cancer

- Intermediate risk favorable – few candidates
  - One of below risk factors
    - Grade Group 2 (Gleason score 3+4)
    - cT2b to cT2c (palpable nodule <1/2 of gland)
    - PSA 10-20
    - <50% biopsy cores positive
  - Considered only in select candidates
    - Low volume

Grade Group

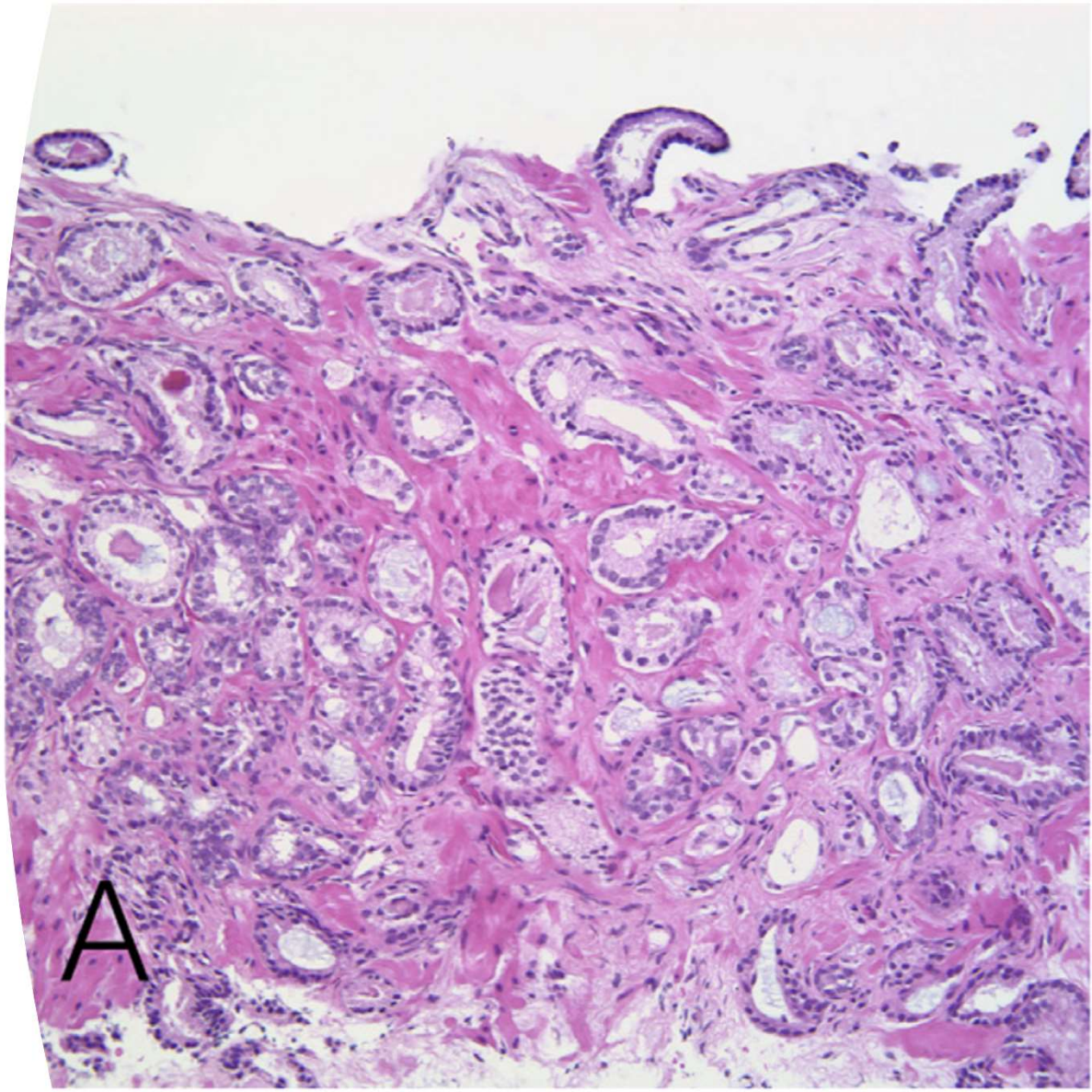
- 2014 ISUP Consensus Conference
  - Introduction of Grade Group System

Gleason Score	Grade Group
3 + 3 = 6	1
3 + 4 = 7	2
4 + 3 = 7	3
4 + 4 = 8	4
4 + 5 = 9, 5 + 4 = 9, 5 + 5 = 10	5

  - Description of percent pattern 4 in reports
  - Removal of cribriform pattern from pattern 3

Gleason Pattern 3

- No expression of basal cell layer in prostatic acini (which differentiates from HGPIN)
- This lack of basal layer allows microinvasion of cells outside prostatic acini
- Allows for invasion of intraprostatic nerve fascia (perineural invasion).
- Rare to extend beyond the prostatic capsule



Can GG1 locally spread?

EUROPEAN UROLOGY 72 (2017) 455–460

Extraprostatic Extension Is Extremely Rare for Contemporary Gleason Score 6 Prostate Cancer

Blake B. Anderson [a,], Daniel T. Oberlin [b], Aria A. Razmaria [a], Bonnie Choy [c], Gregory P. Zagaja [a], Arieh L. Shalhav [a], Joshua J. Meeks [b], Ximing J. Yang [d], Gladell P. Paner [a,c,†], Scott E. Eggener [a,†]*

[a] Section of Urology, University of Chicago, Chicago, IL, USA; [b] Department of Urology, Northwestern University Feinberg School of Medicine, Chicago, IL, USA; [c] Department of Pathology, University of Chicago, Chicago, IL, USA; [d] Department of Pathology, Northwestern University Feinberg School of Medicine, Chicago, IL, USA

7,817 patients underwent radical prostatectomy between 2003-2014

2,502 patients with GG1 prostate cancer

On initial path review:

- 55 T3a (2.2%)
- 5 T3b (0.19%)

Secondary review (accounting for 2014 ISUP updates):

7 T3a, all focal EPE (0.28%)

0 T3b→ No SV invasion

Can GG1 metastasize ?

Am J Surg Pathol. 2012 September ; 36(9): 1346–1352. doi:10.1097/PAS.0b013e3182556dcd.

DO ADENOCARCINOMAS OF THE PROSTATE WITH GLEASON SCORE (GS) ≤6 HAVE THE POTENTIAL TO METASTASIZE TO LYMPH NODES?

Hillary M. Ross[1], **Oleksandr N. Kryvenko**[4], **Janet E. Cowan**[5], **Jeffry P. Simko**[5,6], **Thomas M. Wheeler**[7], and **Jonathan I. Epstein**[1,2,3]

- Review of prostatectomy specimens at 4 academic centers
  - 14,123 cases
    - 22 cases of positive LN
    - 19 cases available for review. All 19 found upgrading of original path based off of updated ISUP Gleason scoring system
    - 0 cases of lymph node metastases

- *Pattern 4 or 5 NECESSARY for metastases*

Low risk Prostate Cancer

- Increasing evidence that men with low risk disease do not require immediate intervention.
  - Risk of metastatic disease is low.
- Vast majority of low risk prostate cancer do not warrant immediate curative treatment

- However, half of Low risk cancers found on standard prostate biopsy have been found to have more significant disease (Gleason score > 6) on radical prostatectomy specimens.

Intermediate Risk Favorable prostate cancer

- Increasing evidence that select men with intermediate risk cancer can be surveilled
  - 1 core only of Grade group 2 disease with <10% involvement with pattern 4
  - Avoid in patients with adverse pathologic features
    - Cribriform pattern
    - Intraductal carcinoma
  - > 1 core of GG2 disease
    - Other co-morbidities
    - Reduced life expectancy

Active Surveillance

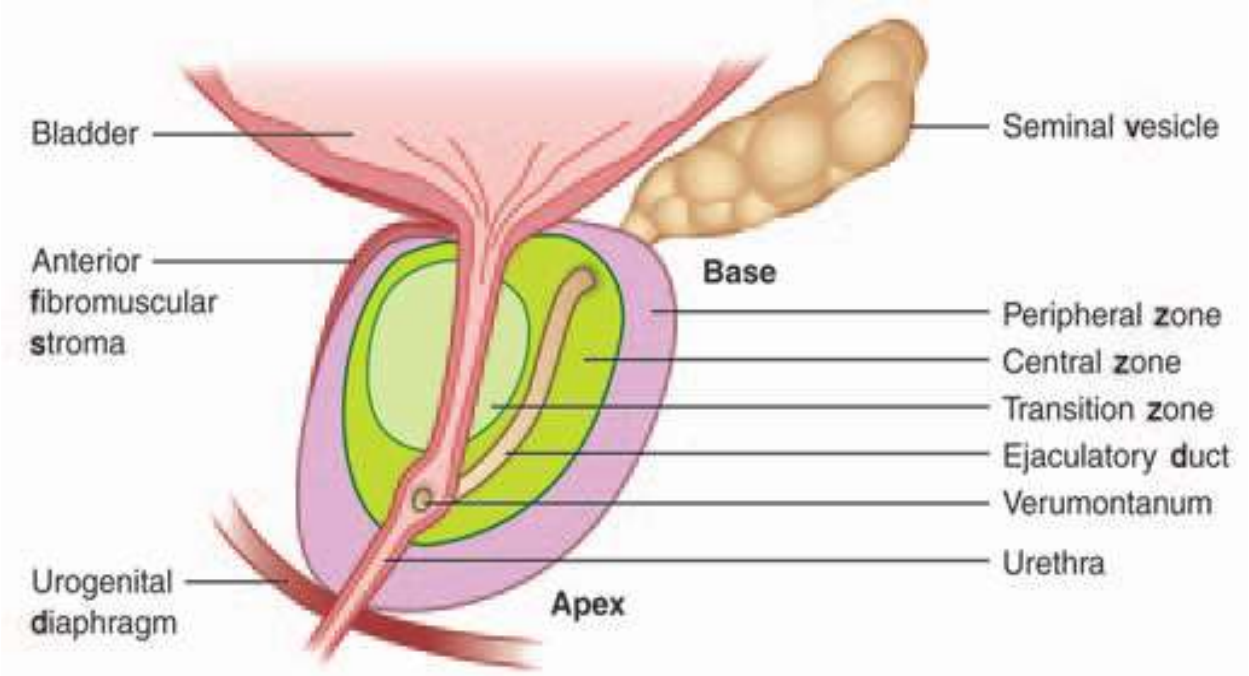
- Excellent option for clinically insignificant prostate cancer (very low, low, intermediate favorable risk)
- Avoids or delays morbidity of definitive curative treatment
  - Erectile Dysfunction
  - Urinary Incontinence
  - Irritative Urinary Symptoms
  - Rectal Toxicity

Active Surveillance

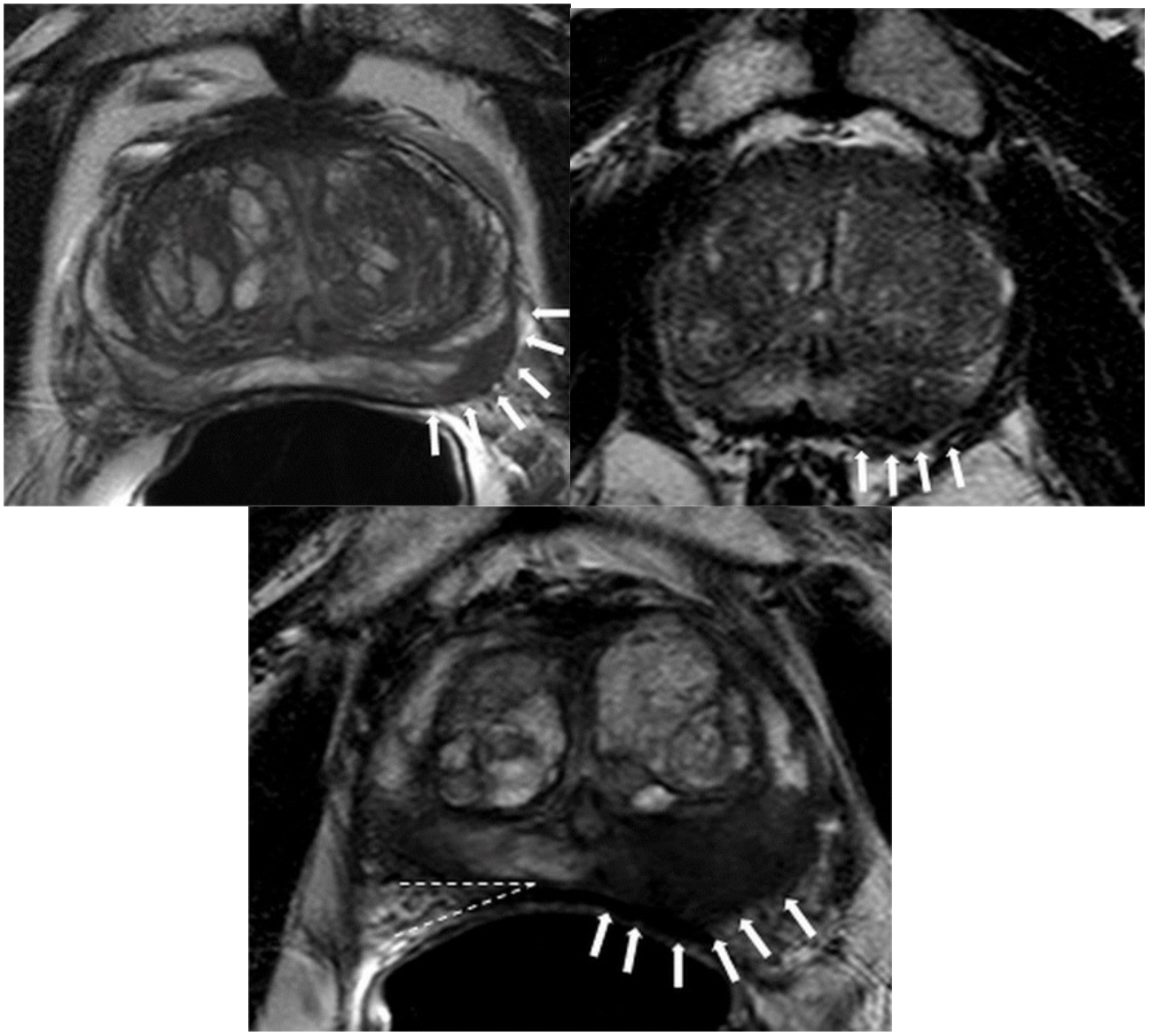
After initial biopsy:

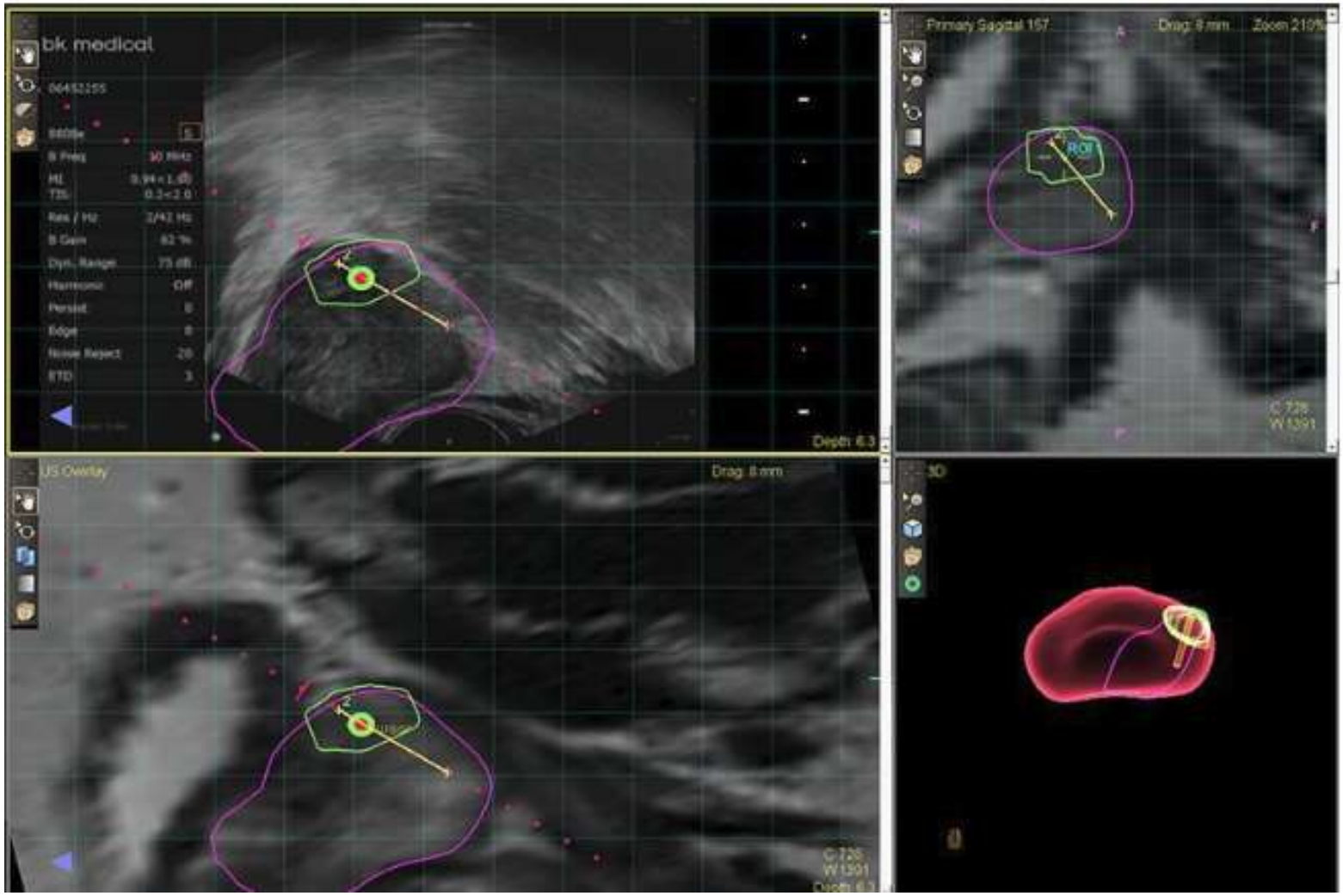
- PSA every 3 months for the first year. Then every 6 months
- mpMRI at 3 or 6 months (if not previously performed)
- Confirmatory prostate biopsy at 6-12 months
- +/- Molecular tumor analysis

mpMRI



- Peripheral zone = 70% (T2 hyperintense)
- Transitional zone = 20% (T2 hypointense)
- Central zone = 1-5%




bk medical
Primary Sagittal 157
Drag: 8 mm
Zoom 210%
ROI
Depth: 6.3
US Overlay
Drag: 8 mm
3D

Active Surveillance

After initial biopsy:

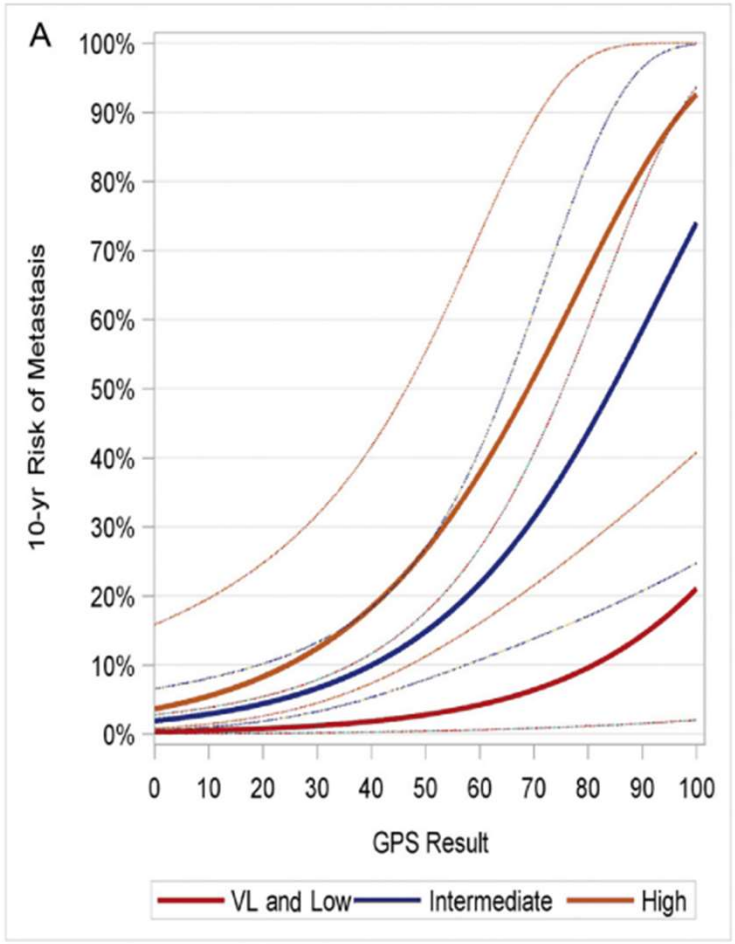
- PSA every 3 months for the first year. Then less frequently
- mpMRI at 3 or 6 months
- Repeat standard prostate biopsy at 6-12 months
- Molecular tumor analysis

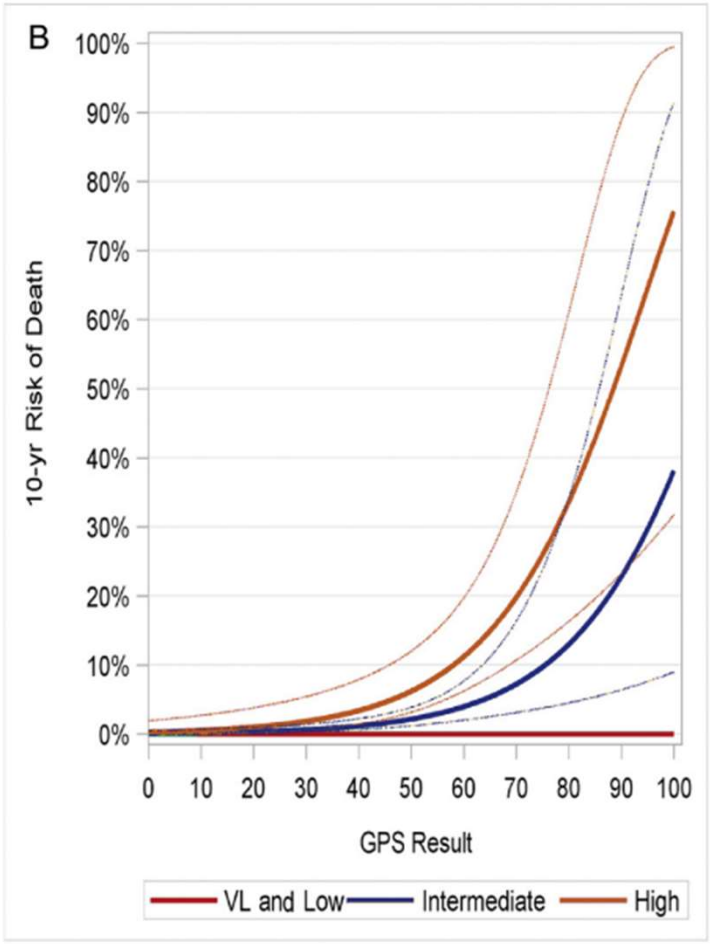
Genomic Studies

Examine gene expression levels dealing with cancer biology within a sample of tumor tissue

Genomic Studies

- Oncotype Dx
  - 17 gene assay +clinical data
  - Androgen signaling, Cellular organization, stromal response, cellular proliferation
- Prolaris
  - 46 gene assay + clinical data
  - Cell cycle Proliferation
- Decipher score
  - 22 gene assay
  - Invasion and metastasis, androgen signaling, metabolism, angiogenesis, growth and differentiation, proliferation and cell death, immune activity and response





- GPS independent predictor of metastases and prostate cancer death

Van Den Eeden et al. *Eur Urol*. 2018.

DECIPHER
PROSTATE BIOPSY

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San Diego, CA 92121
Tel 1.888.792.1601 | Fax 1.855.324.2768
customersupport@genomedx.com | www.genomedx.com

DECIPHER BIOPSY REPORT

PATIENT DETAILS

Patient Name:
MRN/Patient ID:
Date of Birth: 1
Date of Biopsy:

Pathology Laboratory:
Pathologist:
Address:

ORDER INFORMATION

Order Date:
Specimen Received Date:
GenomeDx Accession ID:
Specimen ID:
Ordering Physician:
Clinic/Hospital Name:
Clinic/Hospital Address:

CLINICAL DETAILS

PSA, Most Recent (ng/mL): **7.1**
Specimen Type: **Needle Biopsy**

NCCN Risk Category: **Intermediate Risk**
# of Positive Cores: **11 (11 of 42 Cores)**

Gleason Score: **3+4**
Clinical Stage: **T1c**

YOUR DECIPHER RESULT: GENOMIC LOW RISK

DECIPHER SCORE: 0.23

Risk at RP - Percent Likelihood	
High Grade Disease (primary Gleason grade 4 or 5)	**12.5%**
5-Year Metastasis	**1.0%**
10-Year Prostate Cancer Specific Mortality	**1.9%**

INTERPRETATION

References on reverse

Clinical studies have shown that men with a Decipher low risk score have a favorable prognosis. Men considering active surveillance with a Decipher low risk score may be suitable candidates for active surveillance. Men considering a definitive therapy may have excellent outcomes when treated with local therapy alone.[x2]

*Average clinical risk refers to the average cohort risk of metastasis at 5 years post radical prostatectomy (RP). The average cumulative incidence of metastasis was 6.8% at 5 years post RP, as reported by Kamrea et al., 2013 from analysis of a cohort of 1,010 men with intermediate and high risk clinical features who received RP as first line treatment at the Mayo Clinic between 2000 and 2006.[x]

Genomic Studies – When to use them?

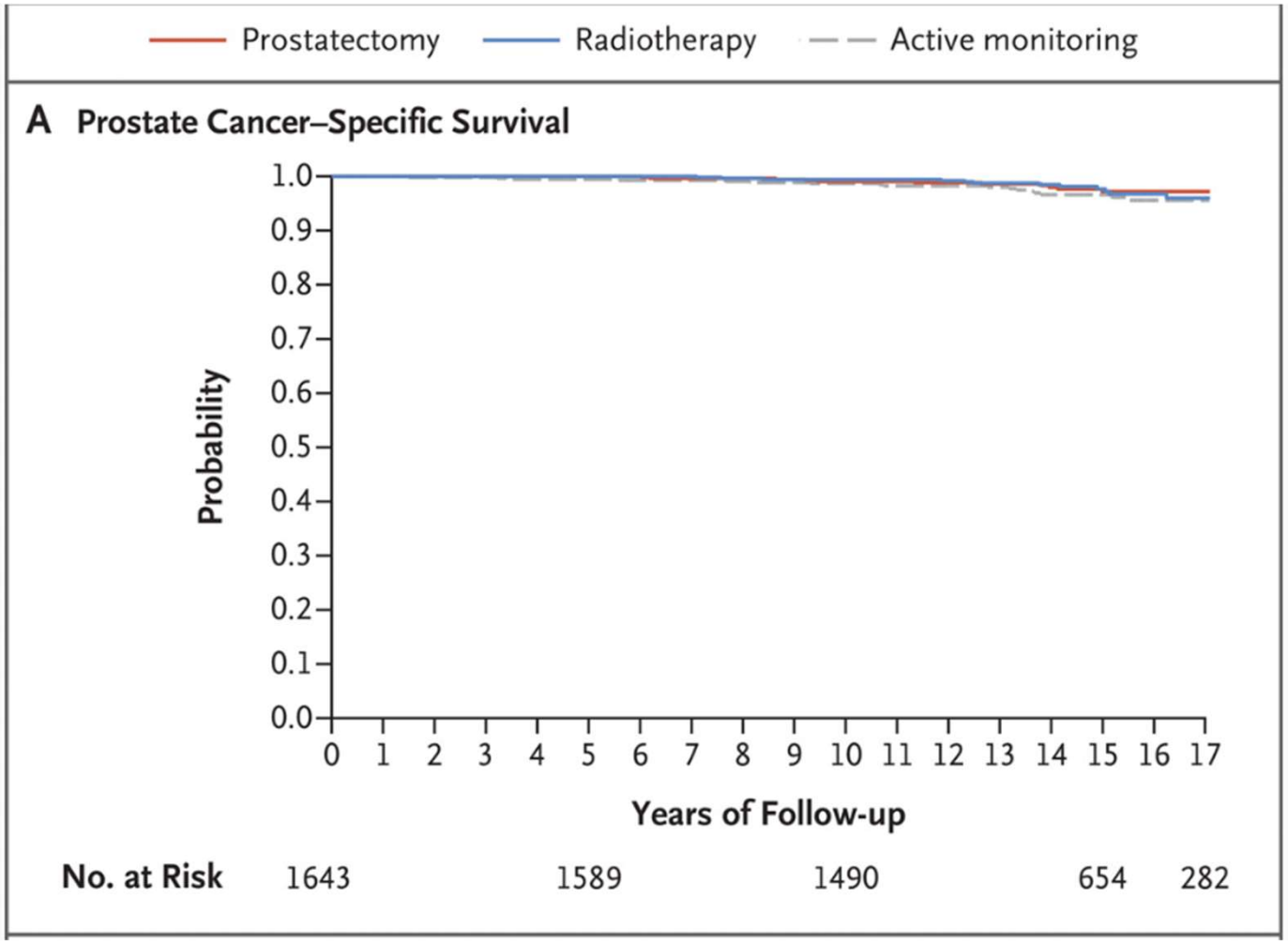
- Very Low risk – Never
- Low risk – seldom
  - If I'm worried about active surveillance
    - High Volume GG1 disease
    - Strong family history
    - Intermediate risk favorable (typically low Pattern 4 component).
    - High PSA

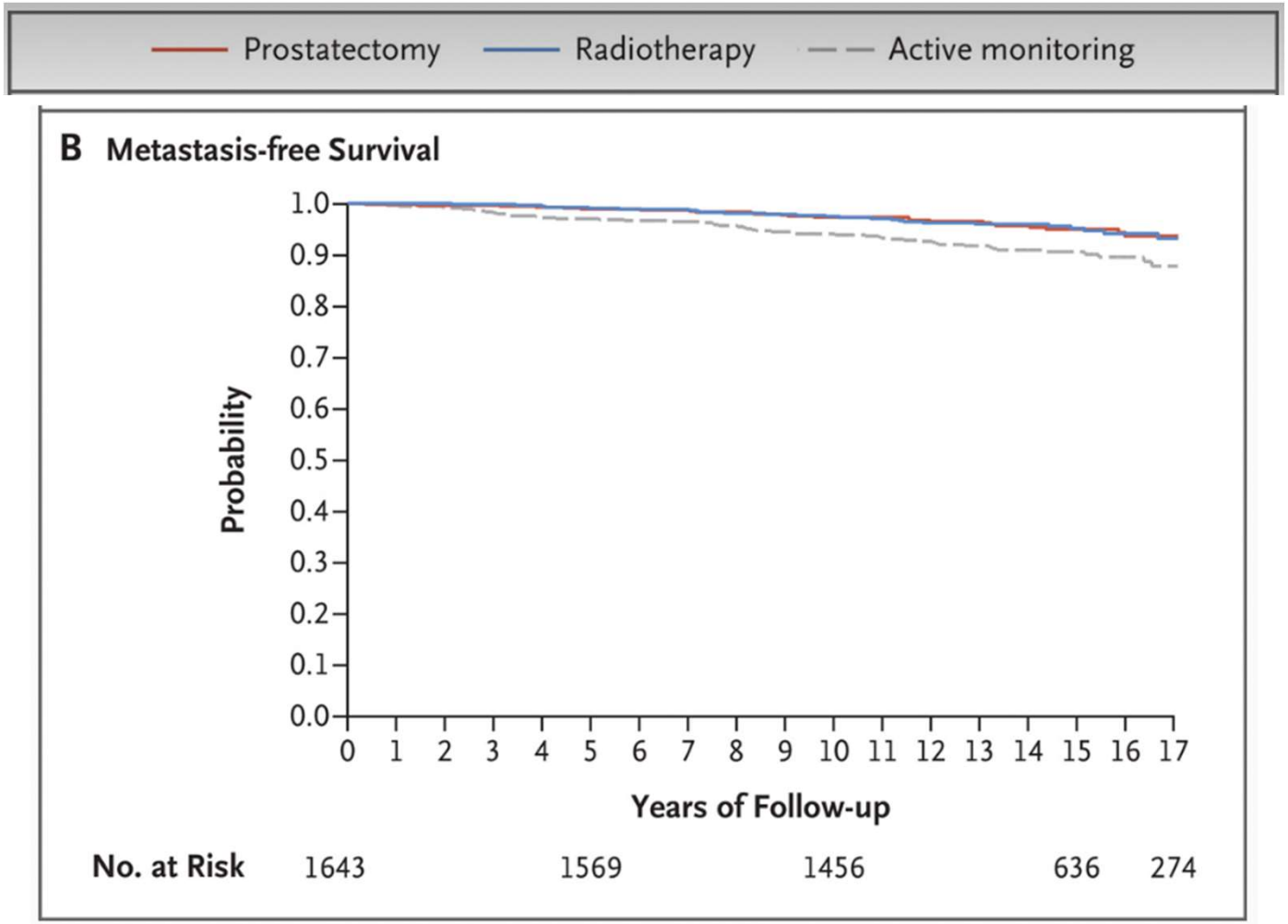
ProtecT trial

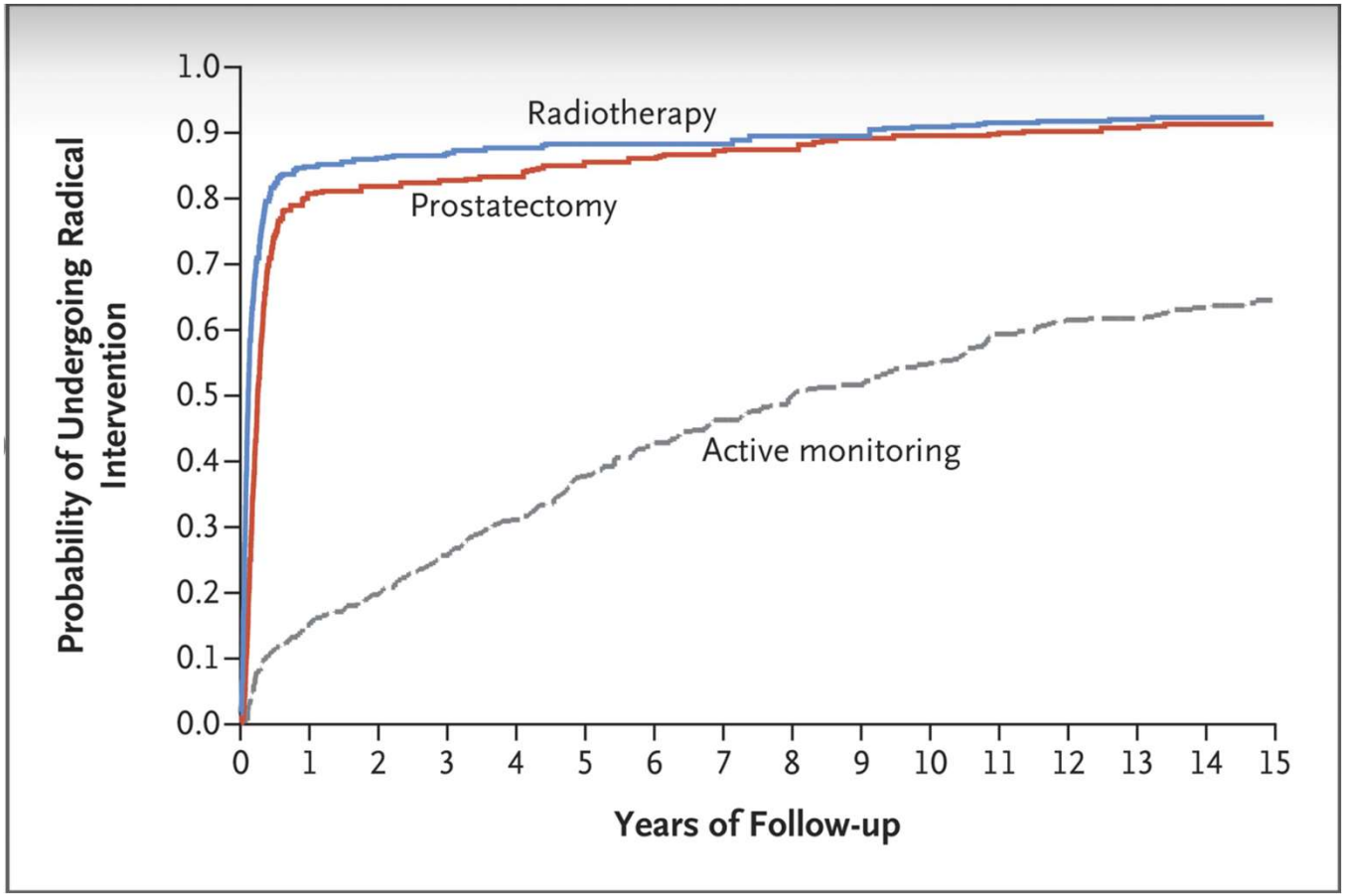
Fifteen-Year Outcomes after Monitoring, Surgery, or Radiotherapy for Prostate Cancer

Hamdy et al. NEJM 2023. 388;1547-1558

- 1643 with localized prostate cancer
  - Median age 62, median PSA 4.6
  - 77% Gleason Score 6
  - 76% T1c
- Randomized to Active surveillance, radiation, or radical prostatectomy


Prostatectomy
Radiotherapy
Active monitoring
A Prostate Cancer–Specific Survival
Probability
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17
Years of Follow-up
No. at Risk
1643
1589
1490
654
282


Prostatectomy
Radiotherapy
Active monitoring
B Metastasis-free Survival
Probability
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17
Years of Follow-up
No. at Risk
1643
1569
1456
636
274


Probability of Undergoing Radical Intervention
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
Radiotherapy
Prostatectomy
Active monitoring
0
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
Years of Follow-up

ProtecT Trial

Fifteen-Year Outcomes after Monitoring, Surgery, or Radiotherapy for Prostate Cancer

Hamdy et al. NEJM 2023. 388;1547-1558

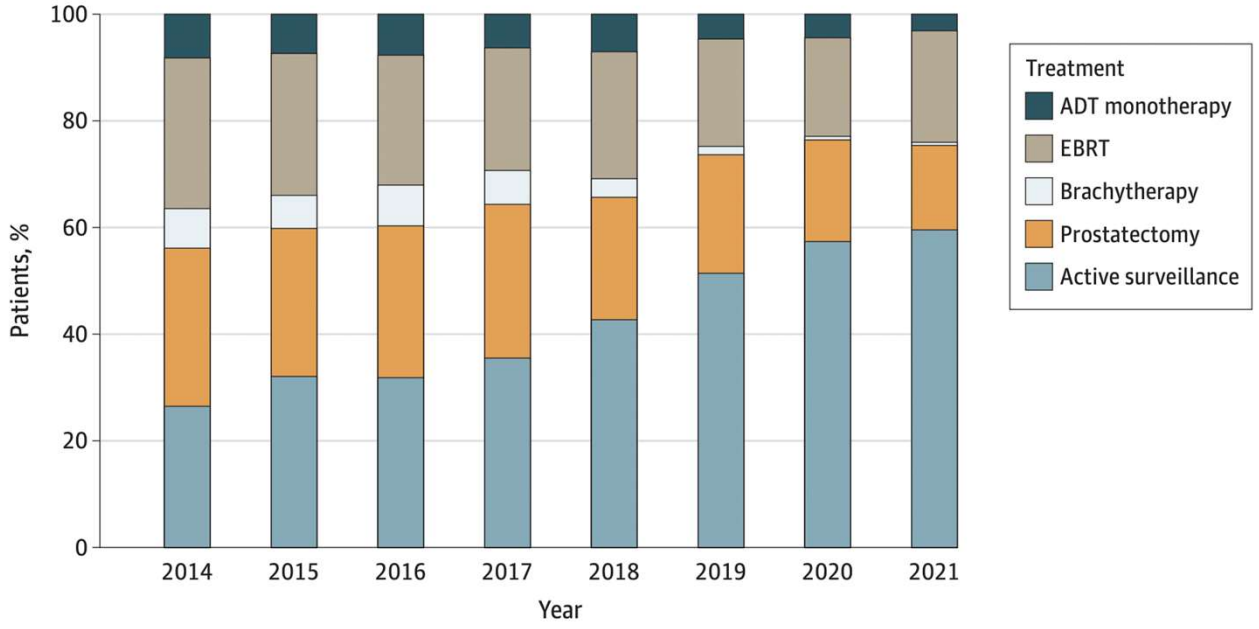
- At 15 yr follow up, death from prostate cancer for active surveillance vs prostatectomy vs radiation:
  - 3.1% vs 2.2% vs 2.9%; p=0.53
- Prostate Cancer-Specific Survival approximately 3% regardless of management
- With active surveillance vs prostatectomy or radiation significantly higher incidence of:
  - metastatic disease: 9.4% vs 4.7% or 5.0%
  - clinical progression: 25.9% vs 10.5% or 11%

Active Surveillance use on the rise

Time Trends and Variation in the Use of Active Surveillance for Management of Low-risk Prostate Cancer in the US

Matthew R. Cooperberg, MD, MPH; William Meeks, MS; Raymond Fang, MSC, MASC; Franklin D. Gaylis, MD; William J. Catalona, MD; Danil V. Makarov, MD, MHS

Figure 1. Treatment of Low-risk Prostate Cancer Over Time



JAMA Network Open. 2023;6(3):e231439. doi:10.1001/jamanetworkopen.2023.1439

Active Surveillance

- Management of choice for low risk prostate cancer
- Reasonable for low volume intermediate favorable risk prostate cancer
- Currently no standard protocol for follow-up but generally includes:
  - Serial PSAs following PSA kinetics
  - +/-DRE
  - MRI
  - +/-molecular tumor analysis
  - surveillance prostate biopsies

Active Surveillance

- Many men on AS will progress on to active treatment without change in cancer specific survival
- Further advances with biomarkers and radiographic studies should help with patient selection and follow up
  - PSMA Pet scan
  - MRI visible vs invisible disease

THANK YOU