# *Prostate Cancer 2018: Are all intermediate risk cases the same?*

*LUCAS NOGUEIRA*

# *Declaração de Conflito de Interesses*

**De acordo com a Resolução 1595/2000 do Conselho Federal de Medicina e RDC 102/2000 da ANVISA, declaro que:**

1. Participo de estudos clínicos patrocinados pelas empresas:

   *Novartis, Janssen, Astellas, Bayer*

2. Atuo como *speaker* de eventos das empresas:

   *Janssen, Bayer, Astra Zeneca, Astellas, Roche*

3. Participo como membro do *advisory board* das empresas:

   *Janssen, Bayer, Astellas, Health Genomics*

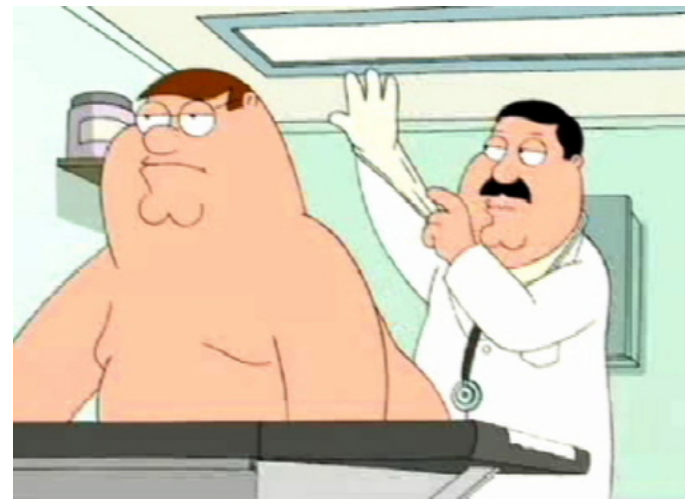
4. Não possuo ações de quaisquer destas companhias farmacêuticas.

Clinically localized disease

- *INDOLENT*
- *INTERMEDIATE AGGRESSIVENESS*
- *AGGRESSIVE*

*Treatment based on the FAILURE RISK*


PSA Test
6.0 ml
Serum Collection Tube
Patient Name
Physician
No.
Pos+
Neg-



# Biochemical Outcome After Radical Prostatectomy, External Beam Radiation Therapy, or Interstitial Radiation Therapy for Clinically Localized Prostate Cancer

Anthony V. D'Amico, MD, PhD; Richard Whittington, MD; S. Bruce Malkowicz, MD; Delray Schultz, PhD; Kenneth Blank, MD; Gregory A. Broderick, MD; John E. Tomaszewski, MD; Andrew A. Renshaw, MD; Irving Kaplan, MD; Clair J. Beard, MD; Alan Wein, MD

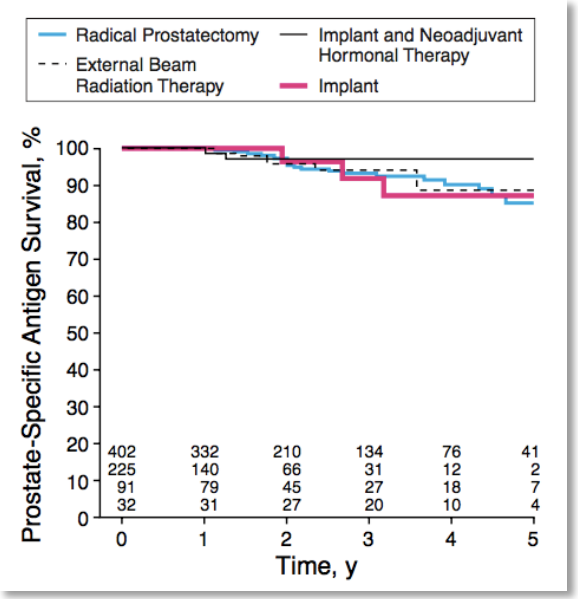
**Original Contribution**

September 16, 1998

UFMG

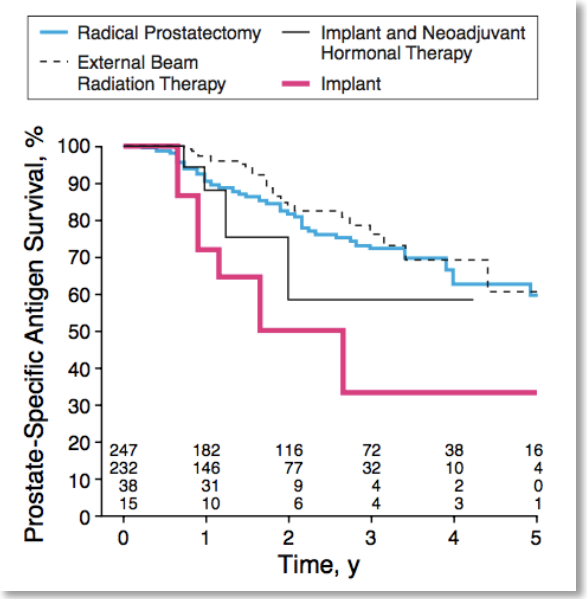
**Low Risk**

T1/T2 *and* Gleason sum ≤ 6 ng/mL *and* PSA ≤ 10 ng/mL



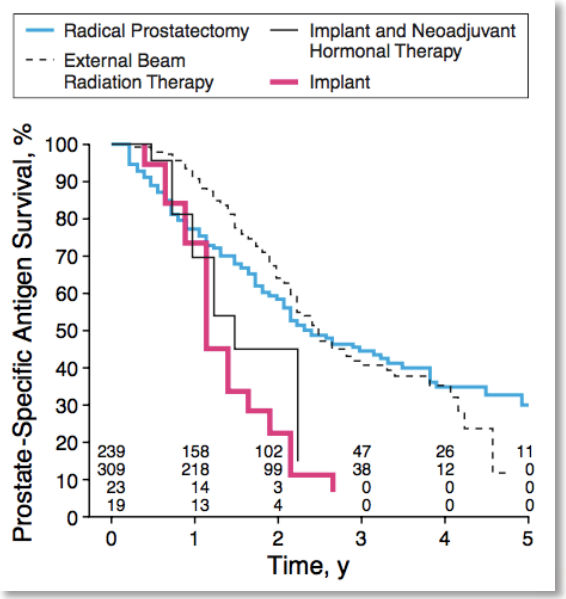

**Intermediate Risk**

T1/T2 *and* Gleason sum = 7 *or* PSA 10.1–20 ng/mL




**High Risk**

PSA > 20 ng/mL *or* Gleason sum ≥ 8



# Biochemical Outcome After Radical Prostatectomy, External Beam Radiation Therapy, or Interstitial Radiation Therapy for Clinically Localized Prostate Cancer

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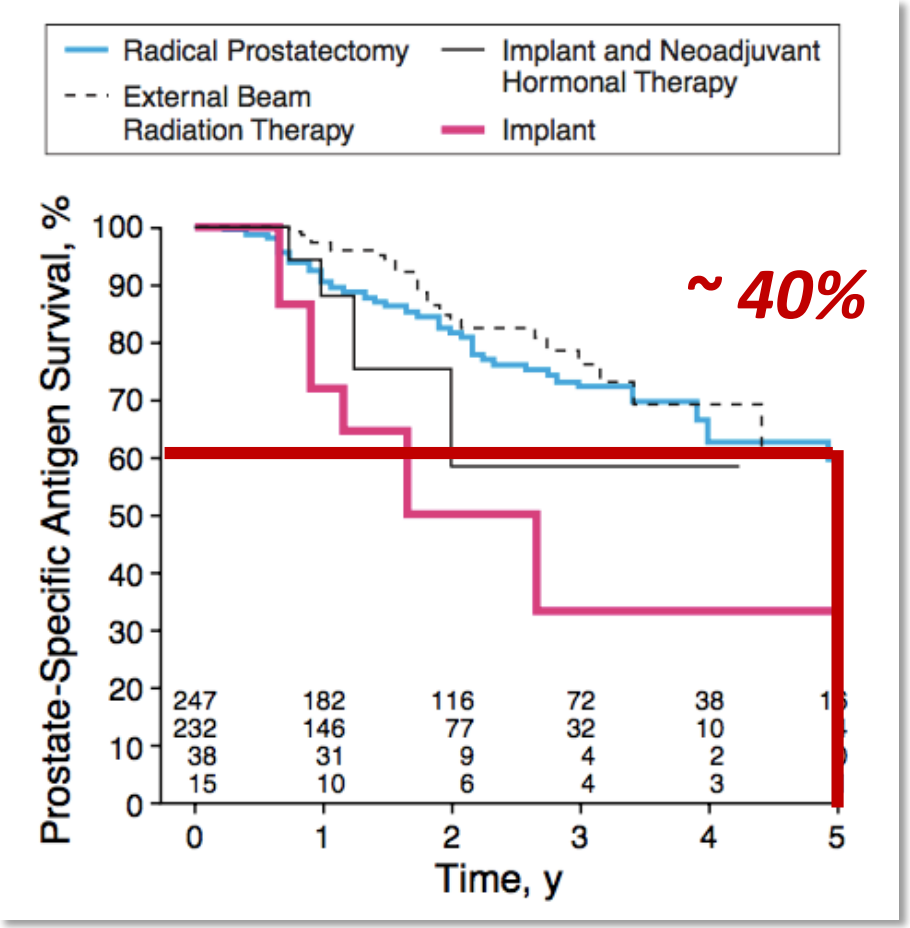
**Intermediate Risk**

T1/T2 *and* Gleason sum = 7
*or* PSA 10.1–20 ng/mL

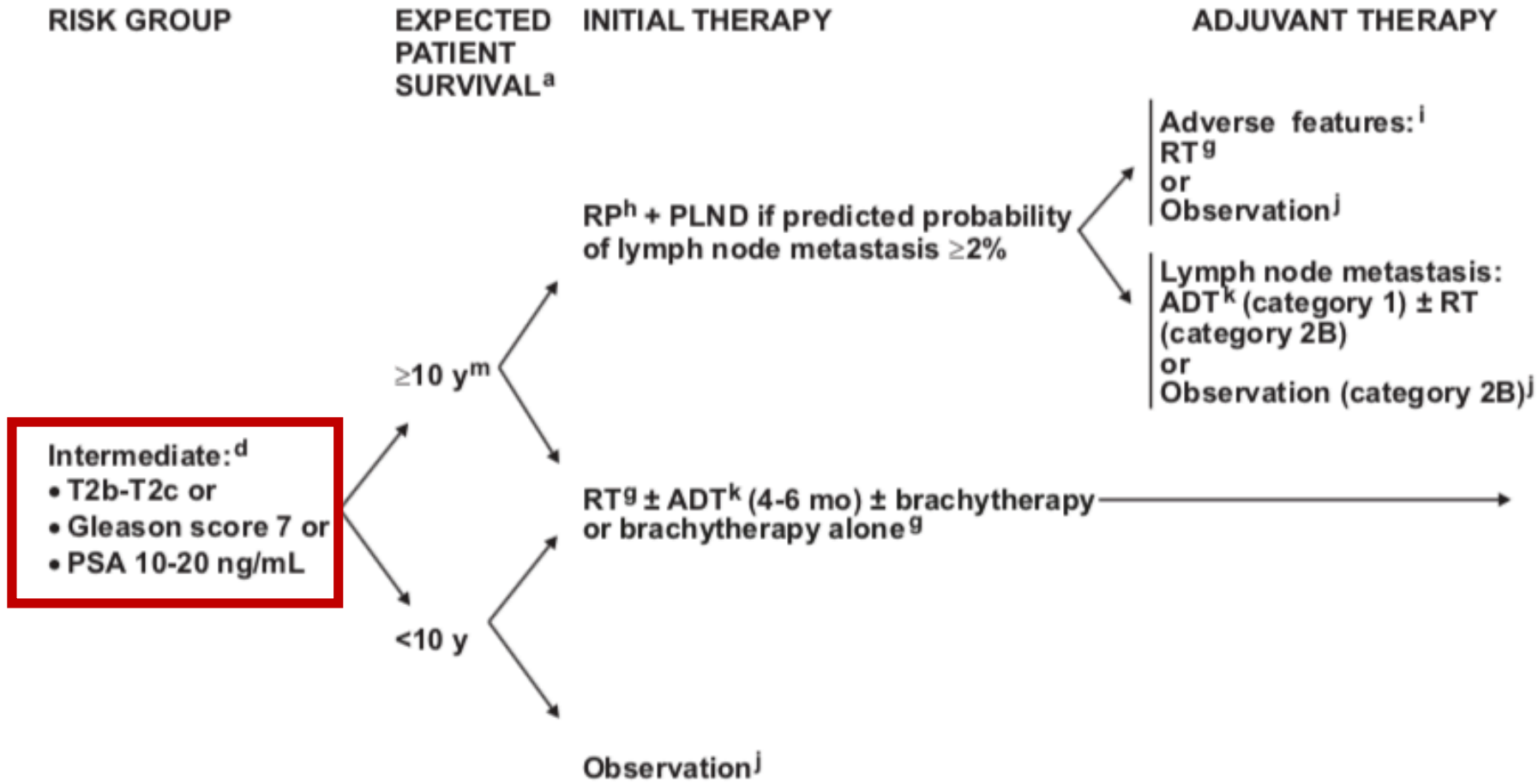



JAMA, September 16, 1998—Vol 280, No. 11

# Prostate Cancer

Version 2.2014

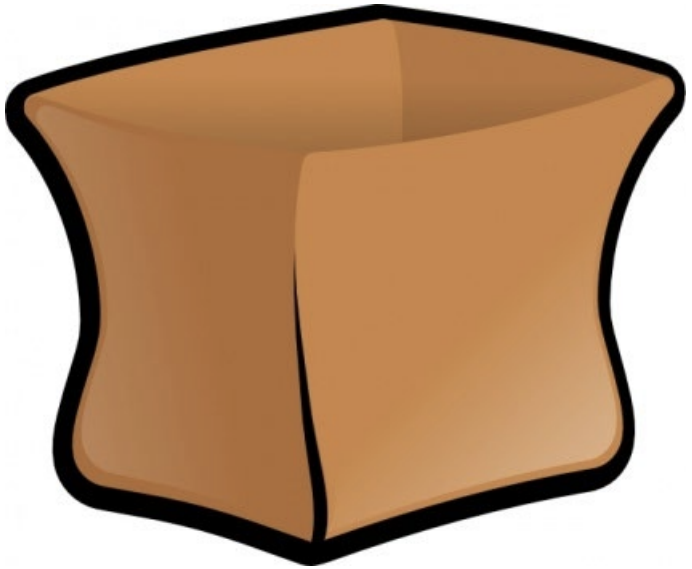
NCCN.org



PSA 10 - 20

Gleason 7

cT2b-c

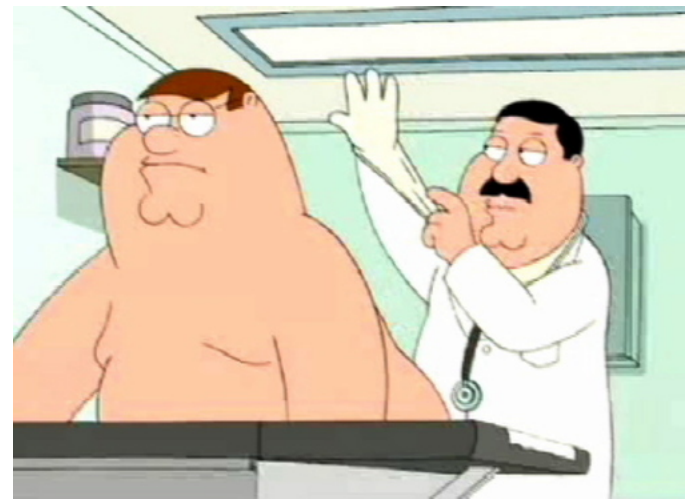



ONE-SIZE FITS ALL
STORE
SALE

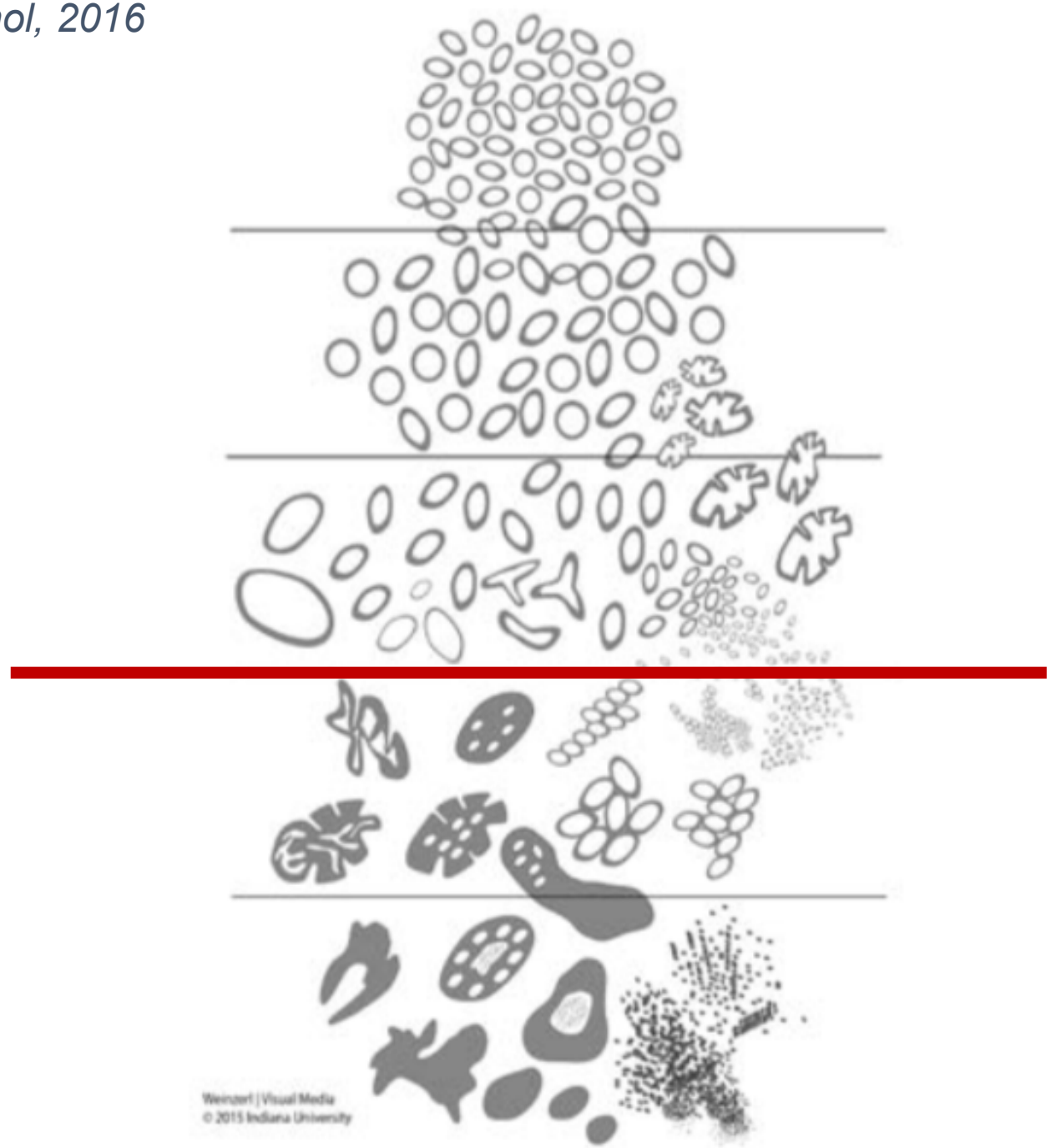
*Should all intermediate risk cases be managed in the same way?*

*NO !!!*


PSA Test
6.0 ml
Serum Collection Tube
Patient Name
Physician
No.
Pos+
Neg-



*Epstein et al, Am J Surg Pathol, 2016*



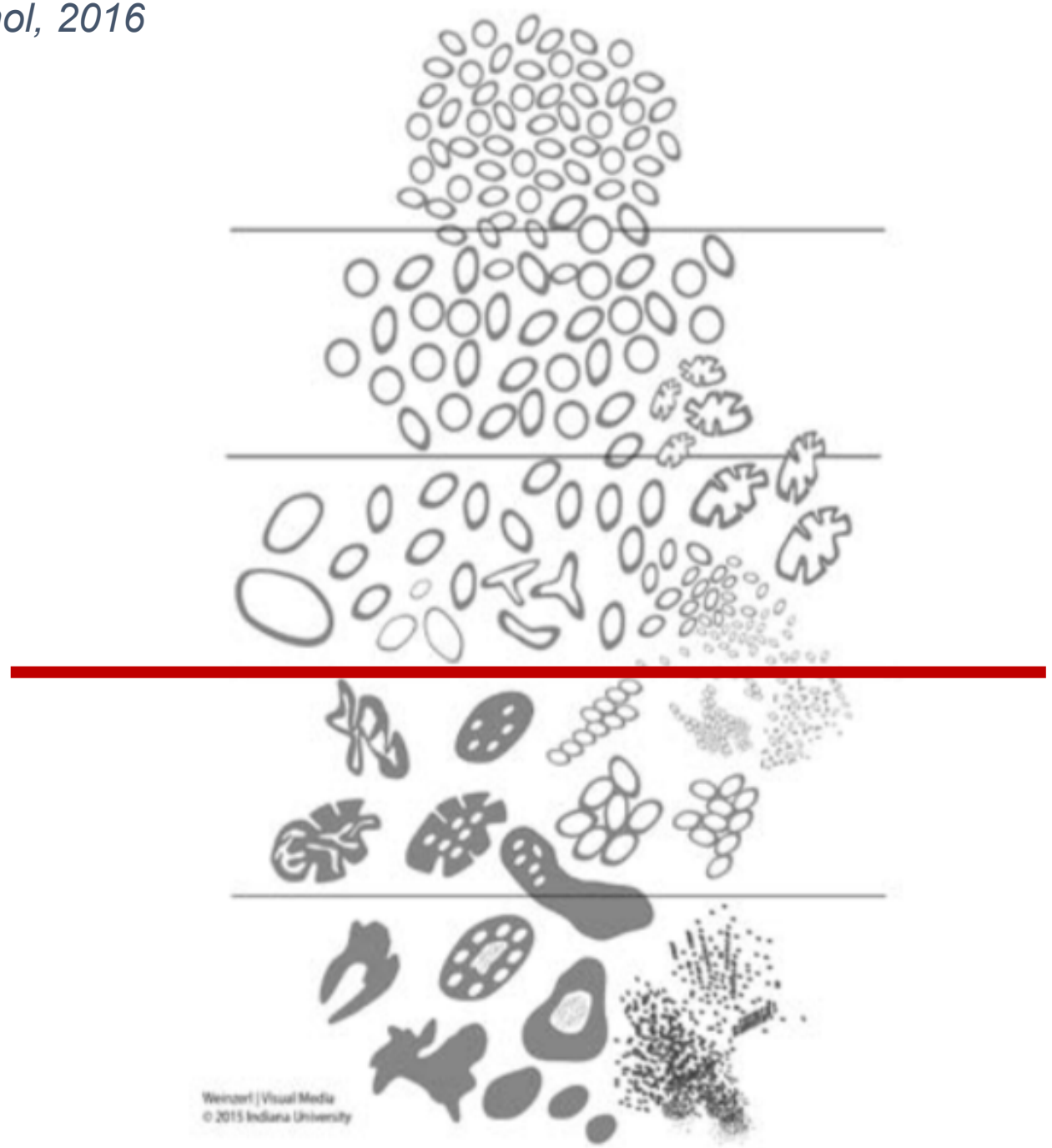

UF m G

# Hallmarks of cancer

| Characteristic/Pathway | Gleason 3 | Gleason4 |
|---|---|---|
| Expression of pro-proliferation embryonic, neuronal, hematopoietic stem cell genes, EGF, EGFR | No | Overexpressed |
| AKT pathway: MAP2K4, RALA, PHLPP, PML | No | Aberrant |
| HER2/neu | No | Amplified |
| Antigrowth signal insensitivity (Cyclin D2, CKDN1β) | Expressed | Absent |
| Resisting apoptosis: DAD1 | Negative | Strong Exp |
| BCL2 | Mostly Neg. | Upregulated |
| Absence of senescence: TMPRSS2-ERG | ERG normal | Increased |
| Sustained angiogenesis: VEGF | Low | Increased |
| Expression of other pro-angiogenic factors | Normal | Increased |
| Tissue invasion/metastasis markers (CXCR4, others) | Normal | Overexpressed |
| PTEN loss | 36% | > 90% |
| Clinical evidence of metastasis/mortality | Absent | Present |

*Klotz, EMUC 2016*

*Epstein et al, Am J Surg Pathol, 2016*




UFMG

# ISUP Grading

| Grade Group | Gleason Score | Gleason Pattern |
|---|---|---|
| 1 | ≤6 | ≤3+3 |
| 2 | 7 | 3+4 |
| 3 | 7 | 4+3 |
| 4 | 8 | 4+4, 3+5, 5+3 |
| 5 | 9 or 10 | 4+5, 5+4, 5+5 |

*Epstein et al, Am J Surg Pathol, 2015*

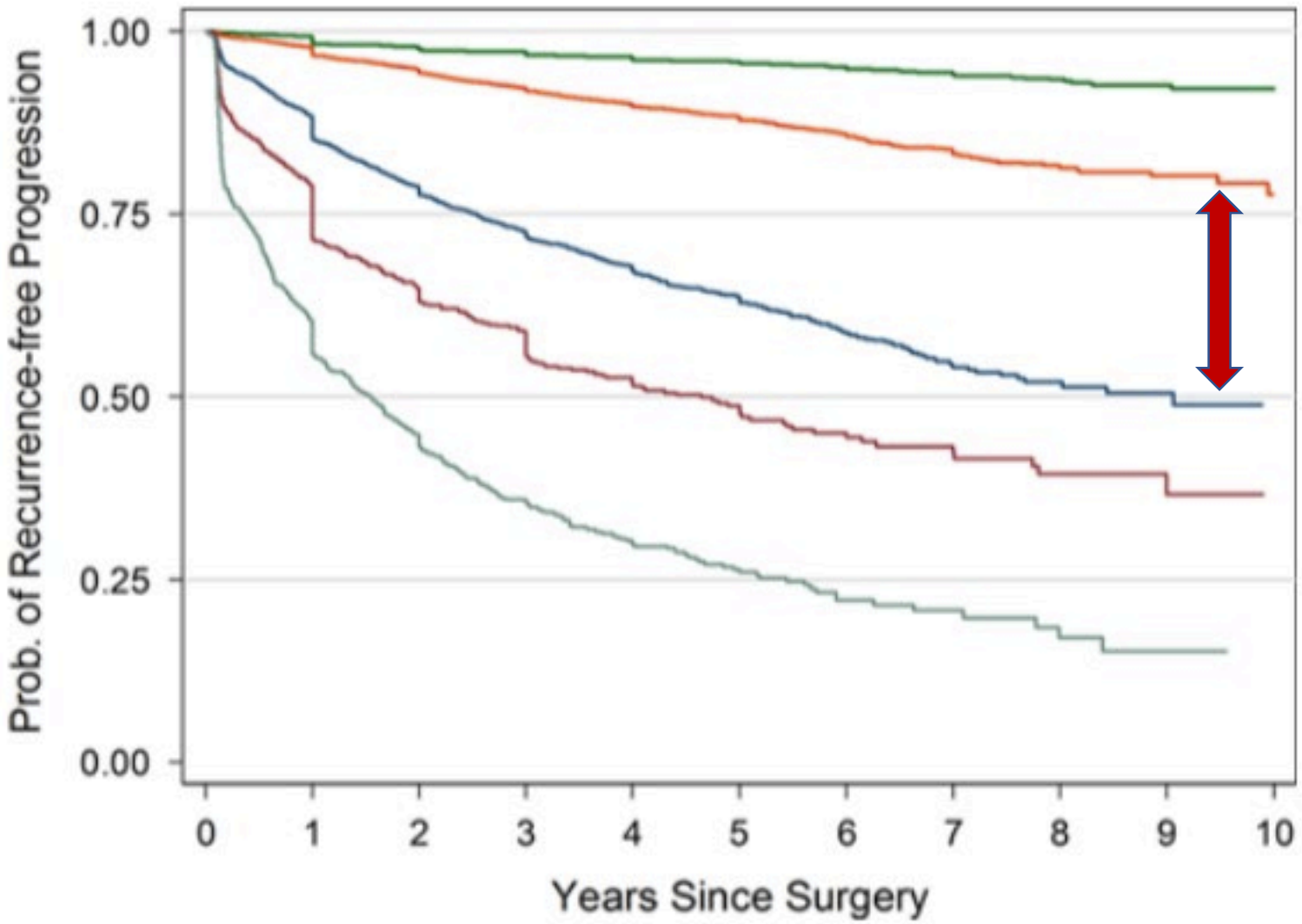
# ISUP Grading

Grade Group 2: Gleason score 3+4=7; predominantly well-formed glands with lesser component of poorly formed/fused/cribriform glands

Grade Group 3: Gleason score 4+3=7; predominantly poorly-formed/fused/cribriform glands with lesser component of well-formed glands

*Epstein et al, Am J Surg Pathol, 2015*

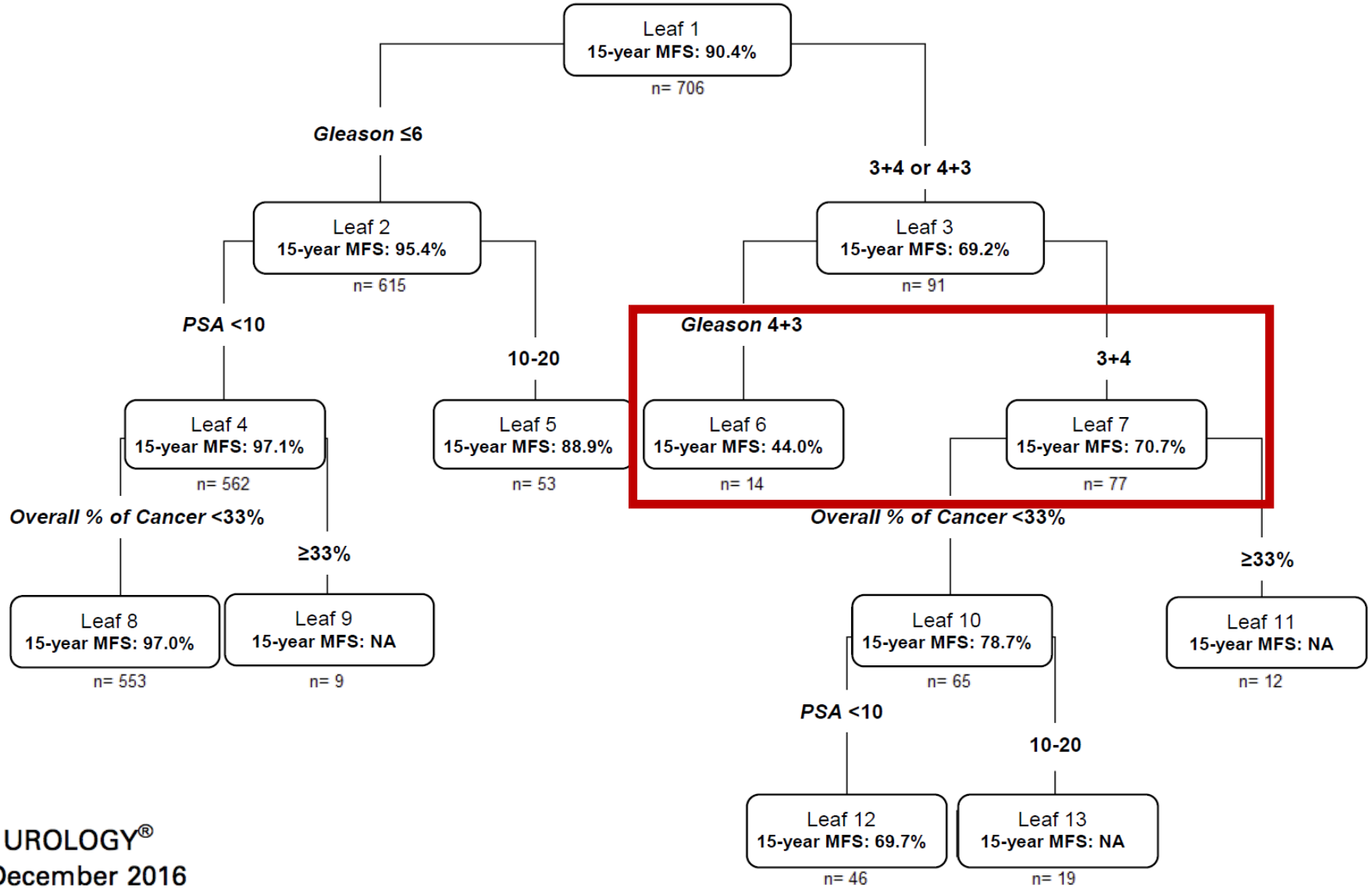
# ISUP Grading




**25%**

*Epstein et al, Am J Surg Pathol, 2015*

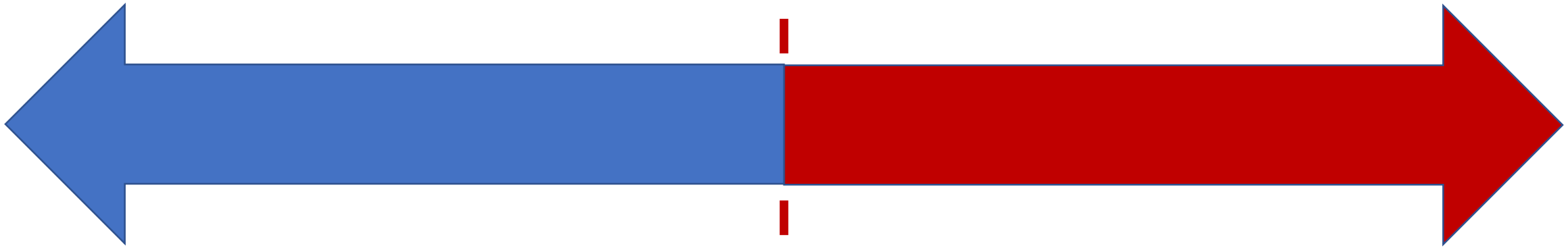
# MFS free survival by risk group




THE JOURNAL OF UROLOGY®
Vol. 196, 1651-1658, December 2016

***ISUP 2***

***ISUP 3***



**Risk of Death From Prostate Cancer After Radical Prostatectomy or Brachytherapy in Men With Low or Intermediate Risk Disease**

Nils D. Arvold,*,† Ming-Hui Chen,† Judd W. Moul,‡ Brian J. Moran,† Daniel E. Dosoretz,† Lionel L. Bañez,† Michael J. Katin,† Michelle H. Bracciforte† and Anthony V. D'Amico†

THE JOURNAL OF UROLOGY®
Vol. 186, 91-96, July 2011

*ISUP 2, <50%, < 2 factors*

Prostate Cancer

Ann C. Raldow, MD[1]; Danjie Zhang, PhD[2]; Ming-Hui Chen, PhD[2]; et al

our results provide evidence to support AS as an initial approach for men with favorable intermediate-risk PC.

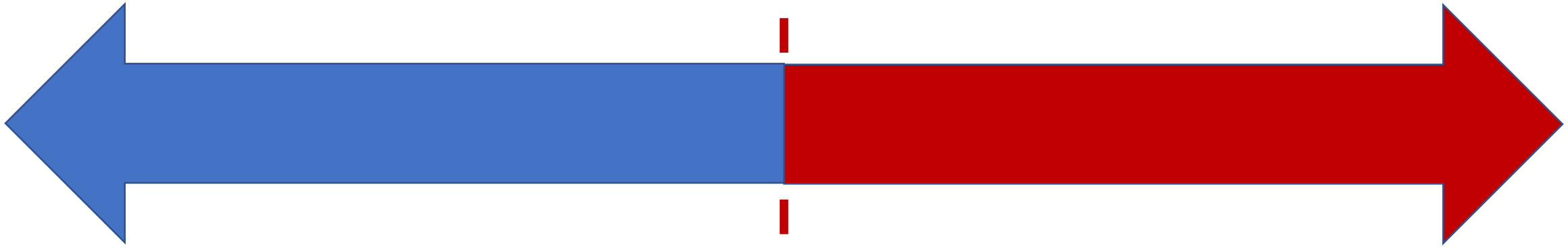
# Prostate Cancer

Version 4.2018 — August 15, 2018

| | |
|---|---|
| Favorable intermediate[g] | • T2b-T2c OR<br>• Gleason score 3+4=7/grade group 2 OR<br>• PSA 10–20 ng/mL<br>AND<br>• Percentage of positive biopsy cores <50% |
| Unfavorable intermediate[g] | • T2b-T2c OR<br>• Gleason score 3+4=7/grade group 2 or Gleason score 4+3=7/grade group 3 OR<br>• PSA 10–20 ng/mL |

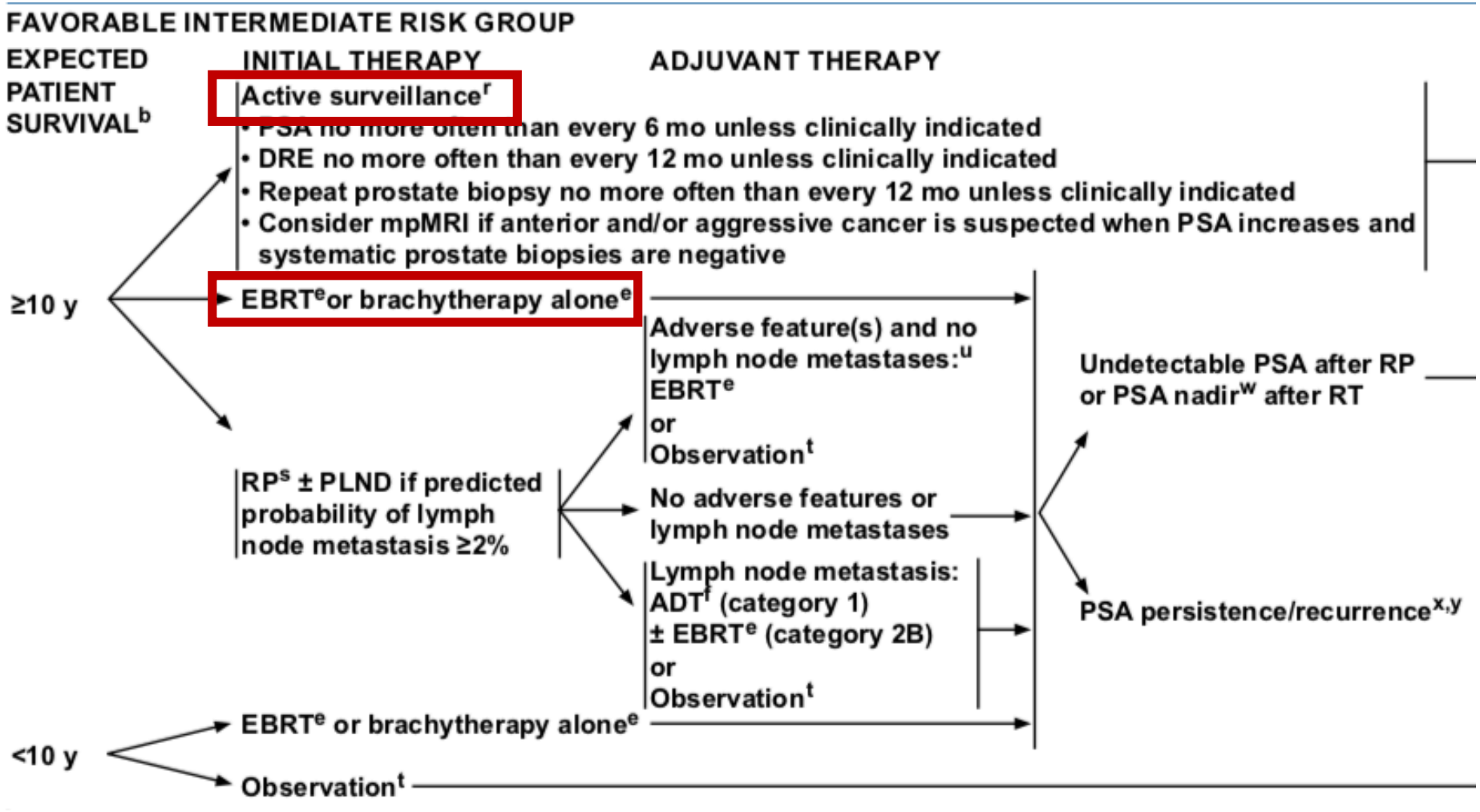
***ISUP 2 < 50%***

***ISUP 2 > 50%***
***ISUP 3***



# Prostate Cancer

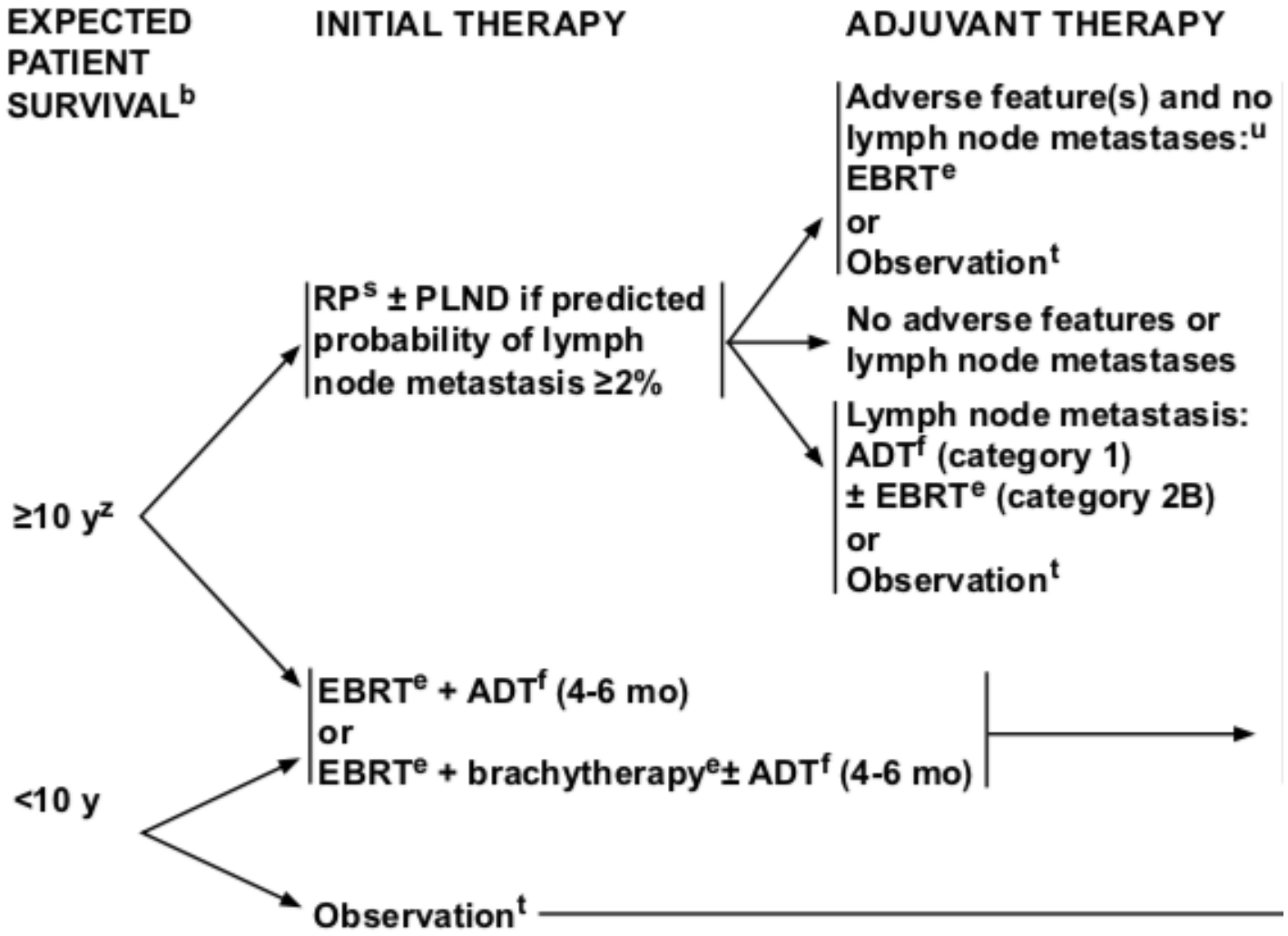
Version 4.2018 — August 15, 2018



# Prostate Cancer

Version 4.2018 — August 15, 2018

## UNFAVORABLE INTERMEDIATE RISK GROUP

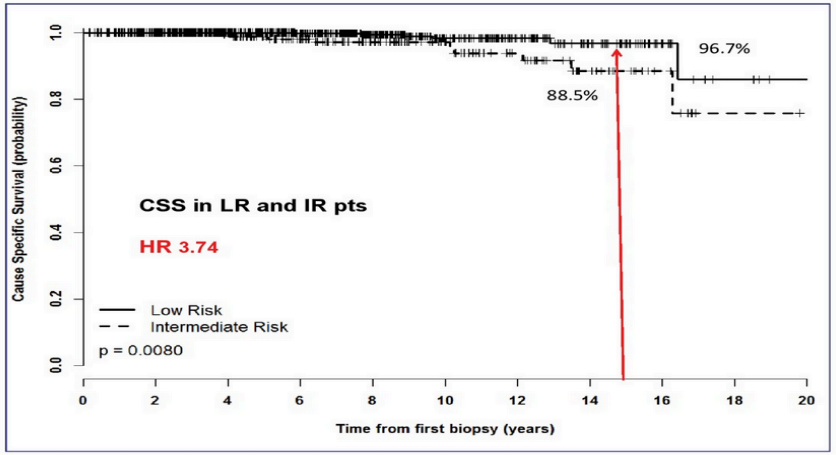


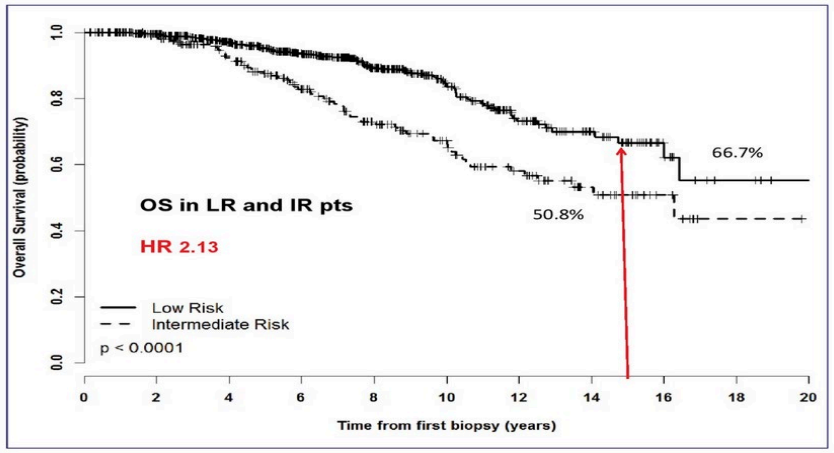
# Cautionary tale of active surveillance in intermediate-risk patients: Overall and cause-specific survival in the Sunnybrook experience.

J Clin Oncol 33, 2015 (suppl 7; abstr 163)

Hima Bindu Musunuru, Laurence Klotz, Danny Vespirini, Liying Zhang, Alexandre

- *945 pts – AS*
  *RI – 237*
  *BR – 708*
- *Tratamento – 34,7% - maioria PSADT – RTX*
- *M+ em 2% BR e 6% RI*
- *IR – risco 4 vezes maior de óbito por CaP*

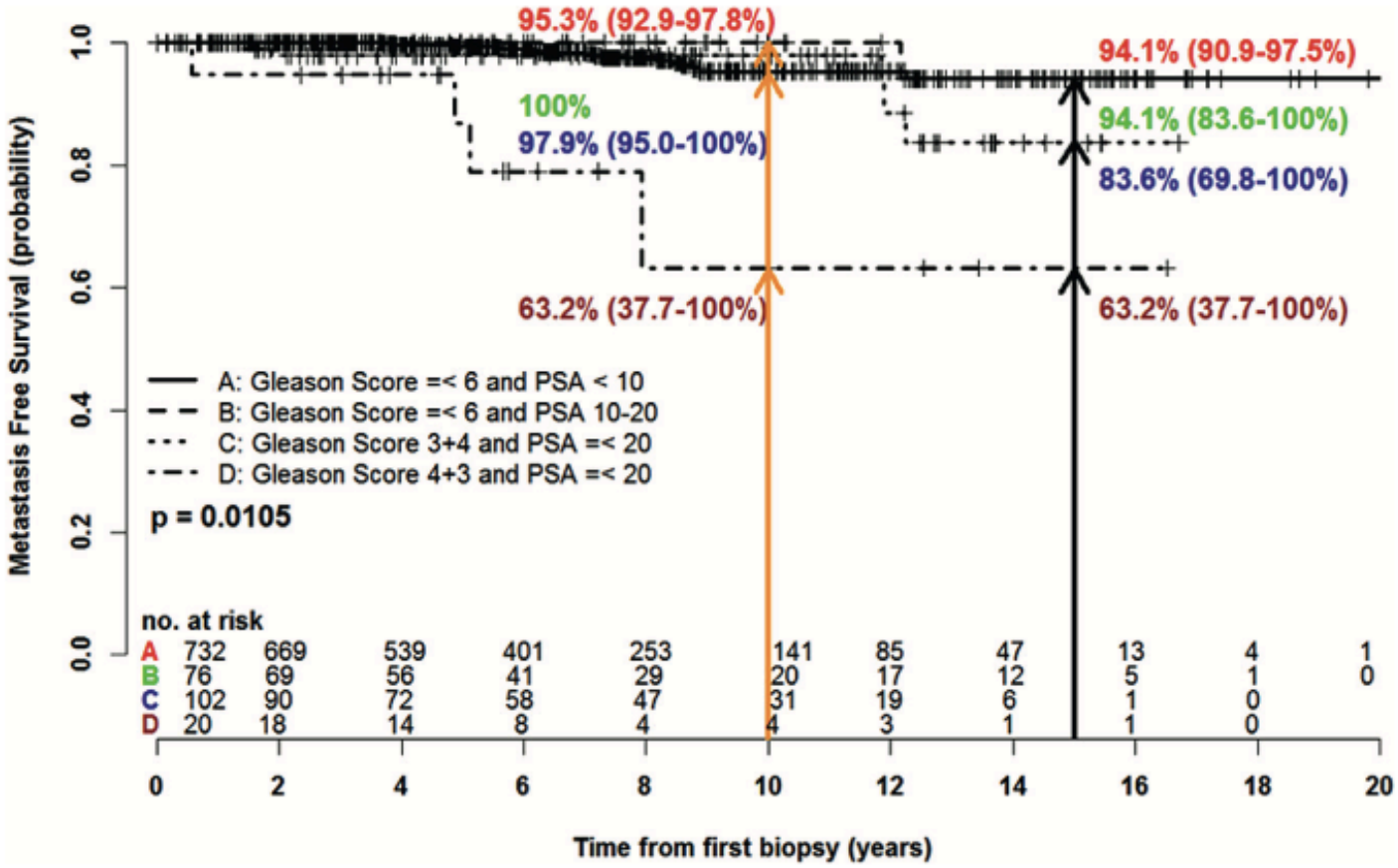



2015 Genitourinary Cancers Symposium

# Active Surveillance for Intermediate Risk Prostate Cancer: Survival Outcomes in the Sunnybrook Experience

Hima Bindu Musunuru, Toshihiro Yamamoto, Laurence Klotz, Gabriella Ghanem, Alexandre Mamedov, Peraka Sethukavalan, Vibhuti Jethava, Suneil Jain, Liying Zhang, Danny Vesprini and Andrew Loblaw*

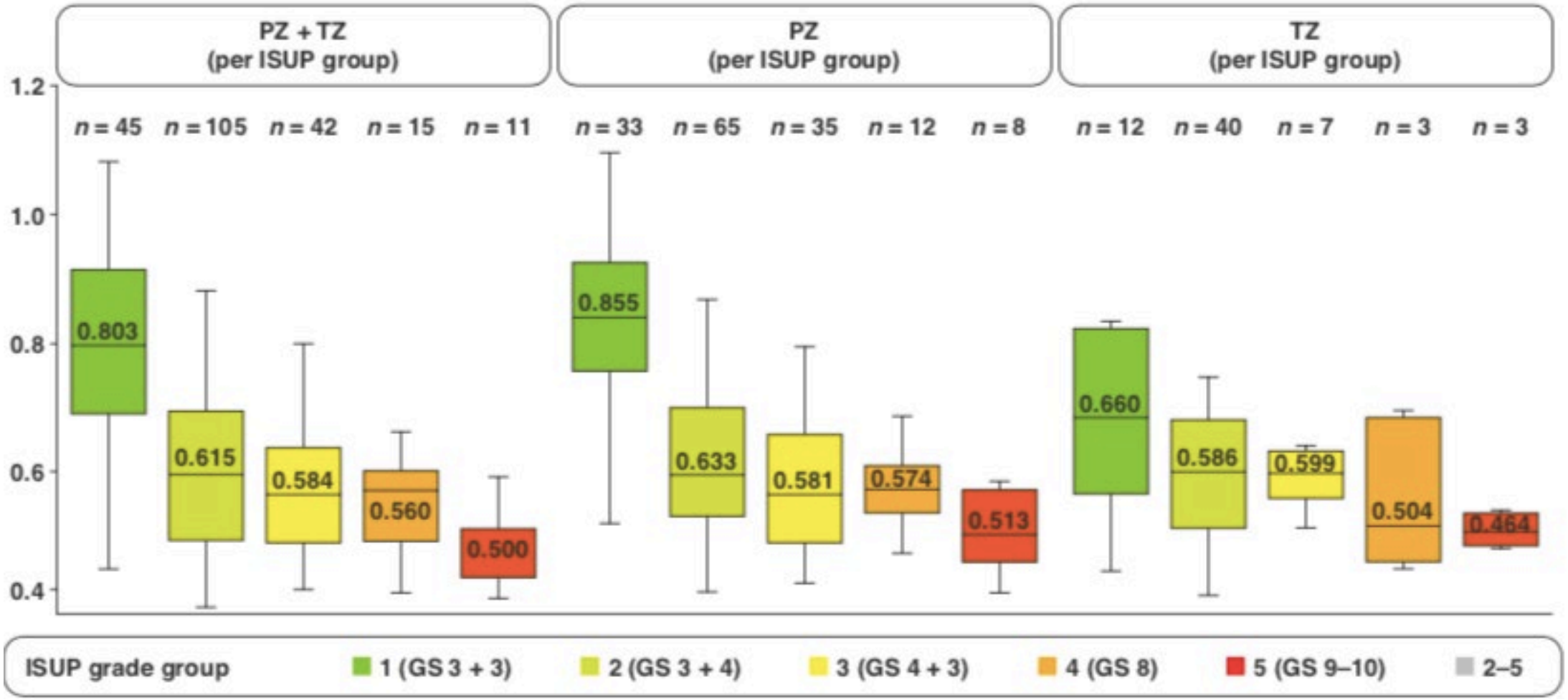



20%

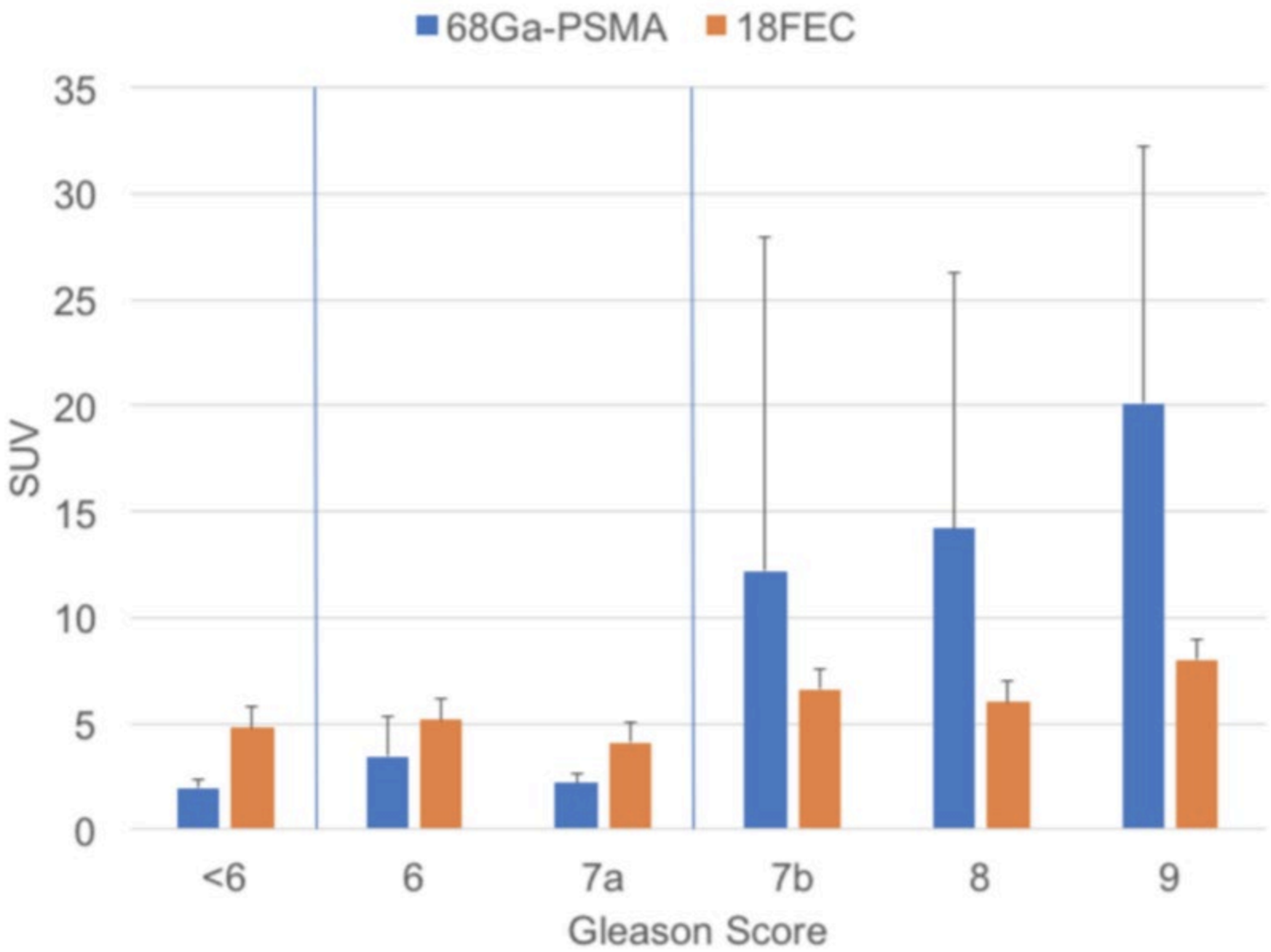
THE JOURNAL OF UROLOGY®
Vol. 196, 1651-1658, December 2016

*Should all intermediate risk cases be managed in the same way?*

# MRI - DWI




AJR, DOI: 10.2214/AJR.18.19937

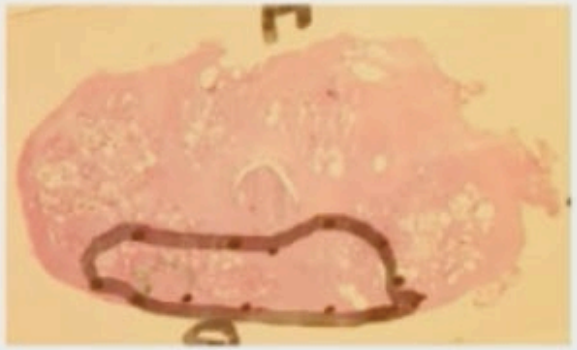



*Hoffman et al, Oncotarget, 2017*

- Phase II Clinical Trial in Prostate Cancer Evaluating 68Ga-PSMA-11 Detection on both Preoperative PET-CT and Immediate Postoperative Specimen Scanning
  - ✓ Prospective, single arm, phase II clinical trial
  - ✓ Gleason grade ≥4+3, negative conventional staging, and scheduled for robotic prostatectomy
  - ✓ $^{68}$Ga-PSMA-11 PET-CT scan for preoperative staging.
  - ✓ $^{68}$Ga-PSMA-11 30-60 min before taking the prostatic pedicle, scanned with a high-resolution (1mm) small bore animal PET scanner.
  - ✓ Whole-mount pathologic processing for intra-lesion analysis and registration with PET imaging.

# Results: PSMA-PET

- For 3+4, PSMA-PET by % pattern 4:
  - 10%: **negative**
  - 20%: positive
  - 30%: positive

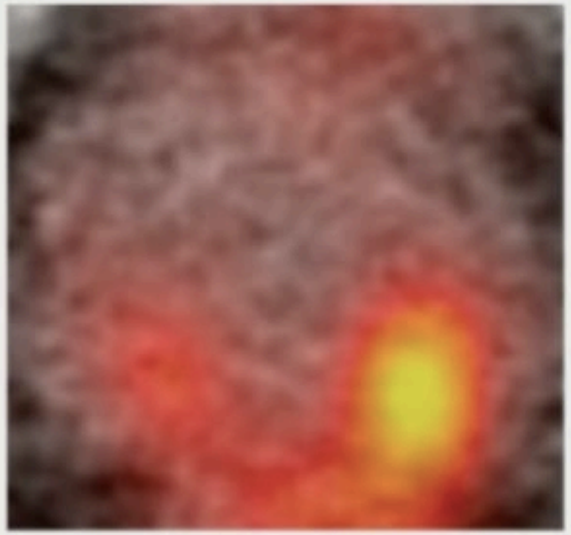


Apex

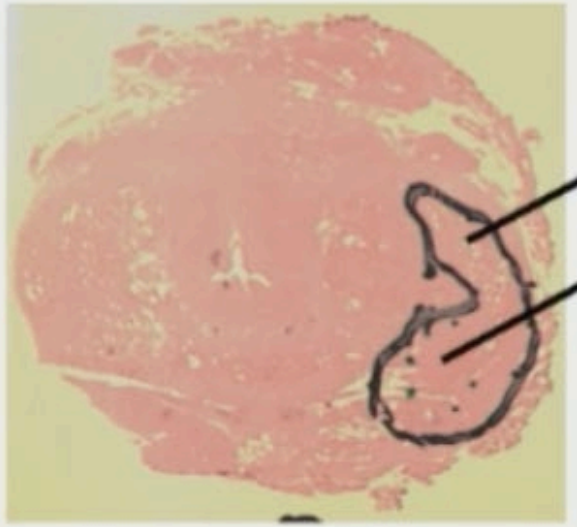
PET negative

90% pattern 3

10% pattern 4



base



PET positive

70% pattern 3

30% pattern 4 clustered

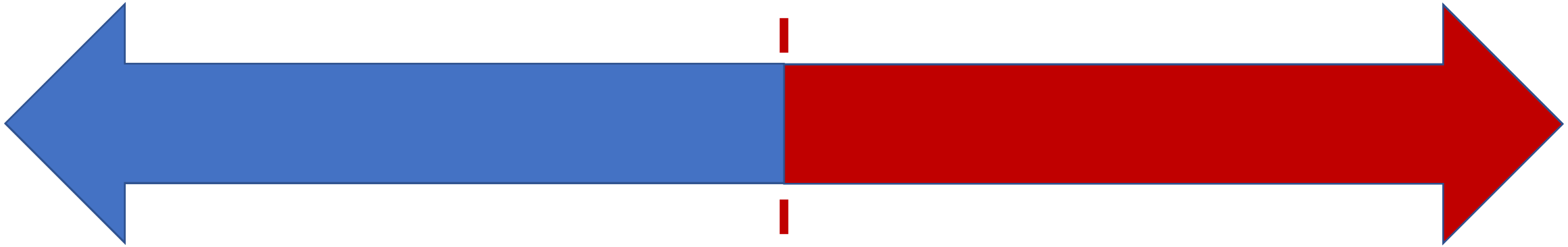
# Cribriform and Intraductal Carcinoma

| | Model without CR/IDC status | | | Model with CR/IDC status | | |
|---|---|---|---|---|---|---|
| | *Adjusted HR* | *95% CI* | *P-value* | *Adjusted HR* | *95% CI* | *P-value* |
| Age (years) | 0.99 | 0.94–1.0 | 0.60 | 0.99 | 0.94–1.0 | 0.63 |
| PSA level ($\log_2$) | 1.2[a] | 1.0–1.5 | 0.02 | 1.2[a] | 1.0–1.5 | 0.04 |
| Percentage of positive cores ($\log_2$) | 1.8[a] | 1.2–2.6 | 0.006 | 1.6[a] | 1.0–2.4 | 0.03 |
| Tumor percentage ($\log_2$) | 1.5[a] | 1.1–2.1 | 0.02 | 1.4[a] | 1.0–2.0 | 0.05 |
| *Gleason score* | | | | | | |
| 6 | | Reference | | | Reference | |
| 3+4=7 | 1.2 | 0.48–3.1 | 0.69 | 0.99 | 0.38–2.6 | 0.99 |
| 4+3=7 | 3.1 | 1.2–8.0 | 0.02 | 1.9 | 0.67–5.4 | 0.23 |
| 8 | 3.7 | 1.4–10 | 0.01 | 2.3 | 0.78–6.9 | 0.13 |
| 9–10 | 5.1 | 2.0–13 | < 0.001 | 3.3 | 1.2–9.3 | 0.02 |
| CR/IDC+ status | | | | 2.6 | 1.4–4.8 | 0.002 |
| Radical prostatectomy | 0.23 | 0.058–0.92 | 0.04 | 0.26 | 0.064–1.0 | 0.05 |
| Radiotherapy | 1.3 | 0.40–4.5 | 0.63 | 1.4 | 0.42–4.7 | 0.58 |

*Kweldam et al, Mod Pathol, 2017*

***ISUP 2 < 50%***

***ISUP 2 > 50%***
***ISUP 3***



**Protocol for the Examination of Specimens From Patients With Carcinoma of the Prostate Gland**

Percentage of Pattern 4 in Gleason Score 3+4=7 Cancer (only if applicable): ____%

+ Percentage of Gleason Patterns 4 and 5 (applicable to Gleason score ≥7) (Note E)
+ Percentage of pattern 4: ____%
+ Percentage of pattern 5: ____%

Conversely, if a minor secondary pattern is of lower grade, it need not be reported. For instance, where there is greater than 95% Gleason pattern 4 and less than 5% Gleason pattern 3, the score should be reported as Gleason score 8(4+4).

*CAP Protocol, 2018*

Percentage of Pattern 4 in Gleason Score 3+4=7 Cancer (only if applicable): ____%

+ Percentage of Gleason Patterns 4 and 5 (applicable to Gleason score ≥7) (Note E)
+ Percentage of pattern 4: ____%
+ Percentage of pattern 5: ____%

percentage of pattern 4 should be recorded in all Gleason score 7(3+4, 4+3) cases.[3] This measurement further stratifies Gleason score 7 and allows identification of cases with limited pattern 4 (eg, <10%) or extensive pattern 4 (eg, >75%).[17]

*CAP Protocol, 2018*

# PSA

| | RP GG 3-5 | | Composite adverse pathology† | |
|---|---|---|---|---|
| | OR | 95% CI | OR | 95% CI |
| Low-risk, not very low due to more than one factor‡ | 1.00 | ( Ref. ) | 1.00 | ( Ref. ) |
| Intermediate-risk: GG 1, PSA 10-15 ng/mL, not VL crit. | 1.26 | (0.84-1.91) | 1.31 | (1.00-1.72) |
| Intermediate-risk: GG 1, PSA 15-20 ng/mL, not VL crit. | 1.99 | (1.17-3.40) | 1.58 | (1.06-2.35) |
| Intermediate-risk: GG 2, PSA <15 ng/mL, VL crit. with <8 mm cancer in 1-4 cores | 2.33 | (1.55-3.51) | 1.05 | (0.75-1.45) |
| Intermediate-risk: GG 2, PSA <15 ng/mL, not VL crit. | 2.87 | (2.23-3.70) | 2.14 | (1.80-2.54) |
| Intermediate-risk: GG 2, PSA 15-20 ng/mL, not VL crit. | 5.89 | (3.88-8.93) | 4.57 | (3.13-6.67) |

*Loeb at al, J Urol 2018 , DOI: 10.1016/j.juro.2018.09.042*

# PSA Kinetics

| | RP GG 3-5 | | Composite adverse pathology† | |
|---|---|---|---|---|
| | OR | 95% CI | OR | 95% CI |
| Low-risk, not very low due to more than one factor‡ | 1.00 | ( Ref. ) | 1.00 | ( Ref. ) |
| Intermediate-risk: GG 1, PSA 10-15 ng/mL, PSAD <0.15 ng/mL/cm3 | 0.34 | (0.05-2.51) | 0.40 | (0.14-1.16) |
| Intermediate-risk: GG 1, PSA 10-15 ng/mL, PSAD >=0.15 ng/mL/cm3 | 1.28 | (0.84-1.94) | 1.35 | (1.03-1.78) |
| Intermediate-risk: GG 1, PSA 15-20 ng/mL, PSAD >=0.15 ng/mL/cm3 | 2.04 | (1.20-3.48) | 1.57 | (1.05-2.35) |
| Intermediate-risk: GG 2, PSA <15 ng/mL, PSAD <0.15 ng/mL/cm3 | 2.52 | (1.89-3.38) | 1.56 | (1.27-1.92) |
| Intermediate-risk: GG 2, PSA <15 ng/mL, PSAD >=0.15 ng/mL/cm3 | 2.97 | (2.29-3.86) | 2.27 | (1.89-2.71) |
| Intermediate-risk: GG 2, PSA 15-20 ng/mL, PSAD >=0.15 ng/mL/cm3 | 5.75 | (3.78-8.75) | 4.50 | (3.08-6.58) |

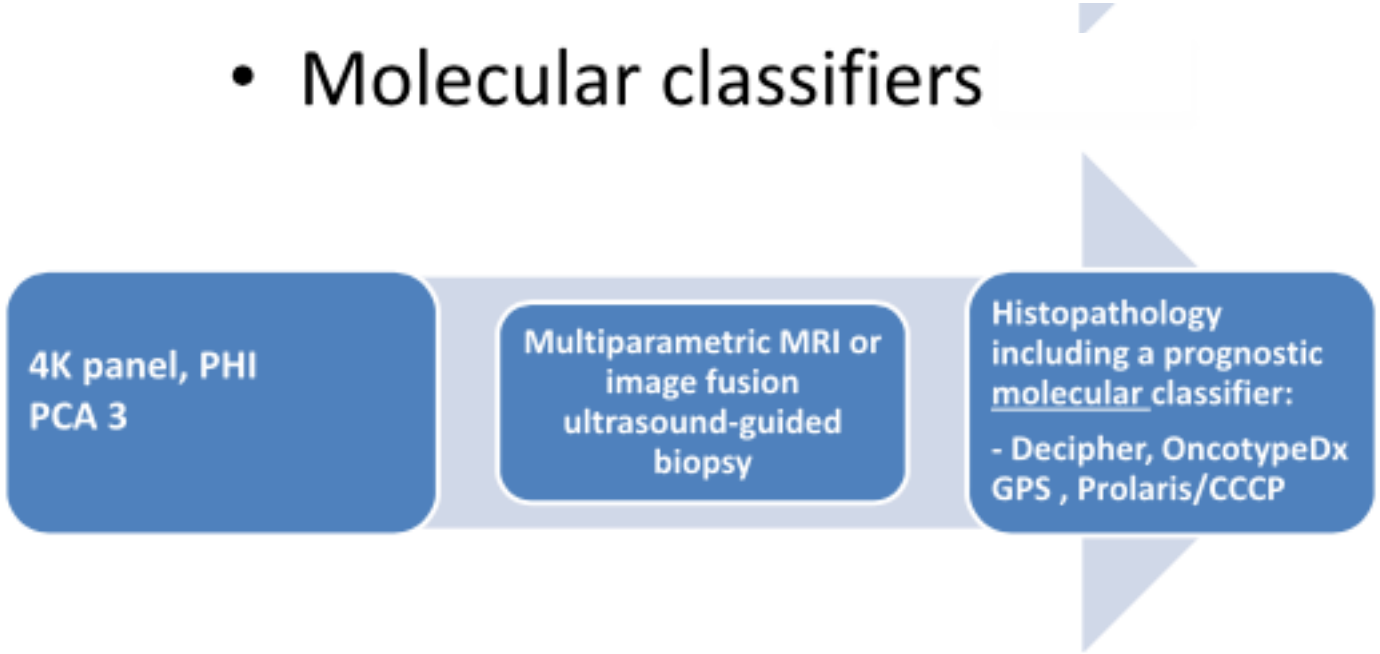
*Loeb at al, J Urol 2018 , DOI: 10.1016/j.juro.2018.09.042*

# The need for a personalized approach for prostate cancer management

JP Michiel Sedelaar* and Jack A Schalken

Sedelaar and Schalken *BMC Medicine* (2015) 13:109
DOI 10.1186/s12916-015-0344-1

- Molecular classifiers



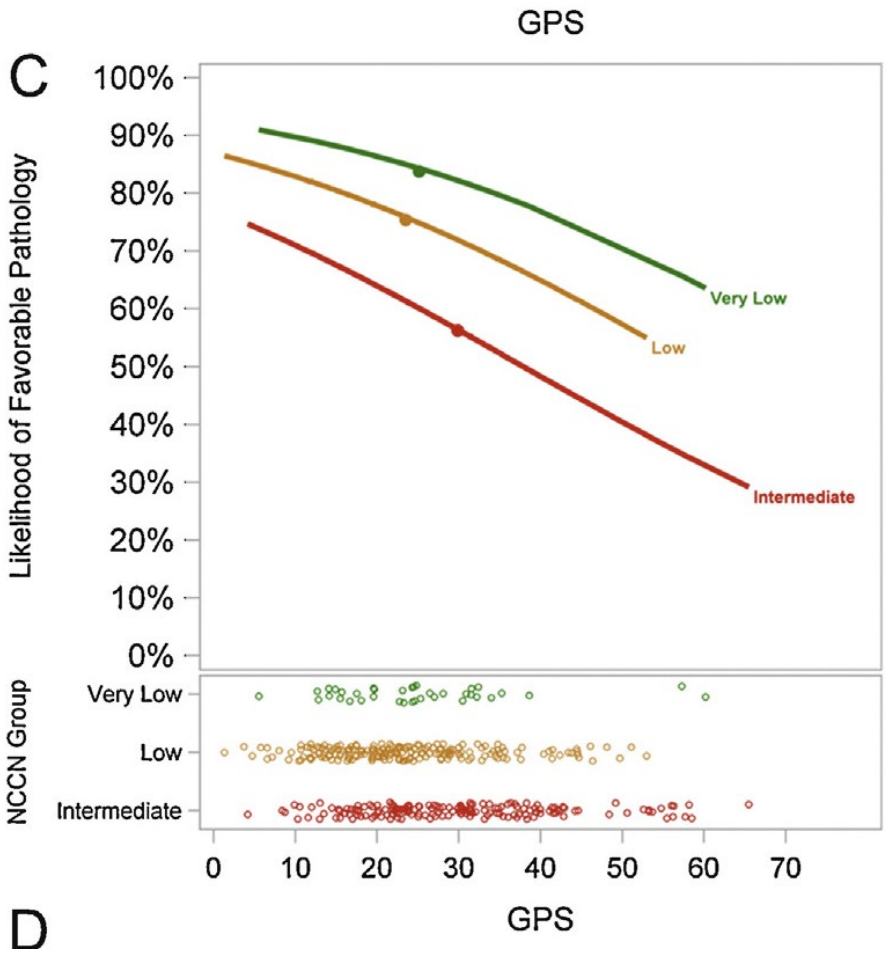
# Genomic Biomarkers

| Test | Platform | Molecular basis | Marketed use | CMS approved use | Useful clinical scenario |
|---|---|---|---|---|---|
| Ki-67 | IHC | Proliferation | NA | No | Watchful waiting |
| Prolaris | RT-PCR | Proliferation | Pre and post local Tx decision making | Yes, decision making for surveillance | Watchful waiting |
| PTEN | IHC/FISH | PTEN | NA | No | Active surveillance |
| ProMark | Quantitative proteomics | Proteins related to PCa adverse pathology and outcomes | Pre-Tx decision making | No | Active surveillance |
| OncotypeDX Prostate | RT-PCR | Transcripts related to PCa adverse pathology and outcomes | Pre-Tx decision making | No | Active surveillance |
| Decipher | RNA MicroArray | Transcripts predictive of PCa metastasis | Post-Tx decision making | Yes, decision making after prostatectomy | Adjuvant radiation |

Abbreviations: FISH, fluorescence *in situ* hybridization; IHC, immunohistochemistry; NA, not available.

# A 17-gene Assay to Predict Prostate Cancer Aggressiveness in the Context of Gleason Grade Heterogeneity, Tumor Multifocality, and Biopsy Undersampling

*Eric A. Klein[a,†,*], Matthew R. Cooperberg[b,c,†], Cristina Magi-Galluzzi[d], Jeffry P. Simko[b,e], Sara M. Falzarano[d], Tara Maddala[f], June M. Chan[b,c], Jianbo Li[f], Janet E. Cowan[b], Athanasios C. Tsiatis[f], Diana B. Cherbavaz[f], Robert J. Pelham[f], Imelda Tenggara-Hunter[b], Frederick L. Baehner[e,f], Dejan Knezevic[f], Phillip G. Febbo[f], Steven Shak[f], Michael W. Kattan[g], Mark Lee[f], Peter R. Carroll[b,**]*




*Klein et al. Eur Urol, 2014*

# Oncotype Dx


Population-Based Clinical Risk Assessment
VERY LOW RISK
10% (N=37)
LOW RISK
49% (N=191)
INTERMEDIATE RISK
41% (N=160)
More Individualized Biologic and Clinical Risk Assessment
VERY LOW RISK
26% (N=100)
LOW RISK
31% (N=119)
INTERMEDIATE RISK
44% (N=169)

*Are all intermediate risk cases the same?*

*Definitely not !!!*

# Summary

UFMG

- Intermediate risk prostate cancer is a very heterogeneous disease, encompassing a wide range of aggressiveness.
- Current risk stratification methods are clearly insufficient to determine the ideal management strategy, as it must be tailored according individual risk factors.
- AS can be offered to a selected group, mainly those with other favorable features.
- Better biomarkers are needed to better risk stratification and management in this group.


GB USA MEX
ONE SIZE
DOES NOT
FIT ALL
30°C
Von links bügeln/ Iron inside out/
repasser sur l'envers /