Surgery or radiotherapy for locally advanced prostate cancer

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A patient

- 65 year old, good performance, no comorbidities
  - PSA 11
  - Gleason 9 at biopsy
  - cT3a on rectal examination (confirmed on MRI)
  - No nodal or distant metastases on imaging.

Would you offer surgery?
Would you offer radiotherapy?
Would you prefer one over the other?

QUALITY
Systematic Reviews
Randomized Controlled Trials
Cohort Studies
Case-Control Studies
Case Series, Case Reports
Editorials, Expert Opinion

What is locally advanced PCa?

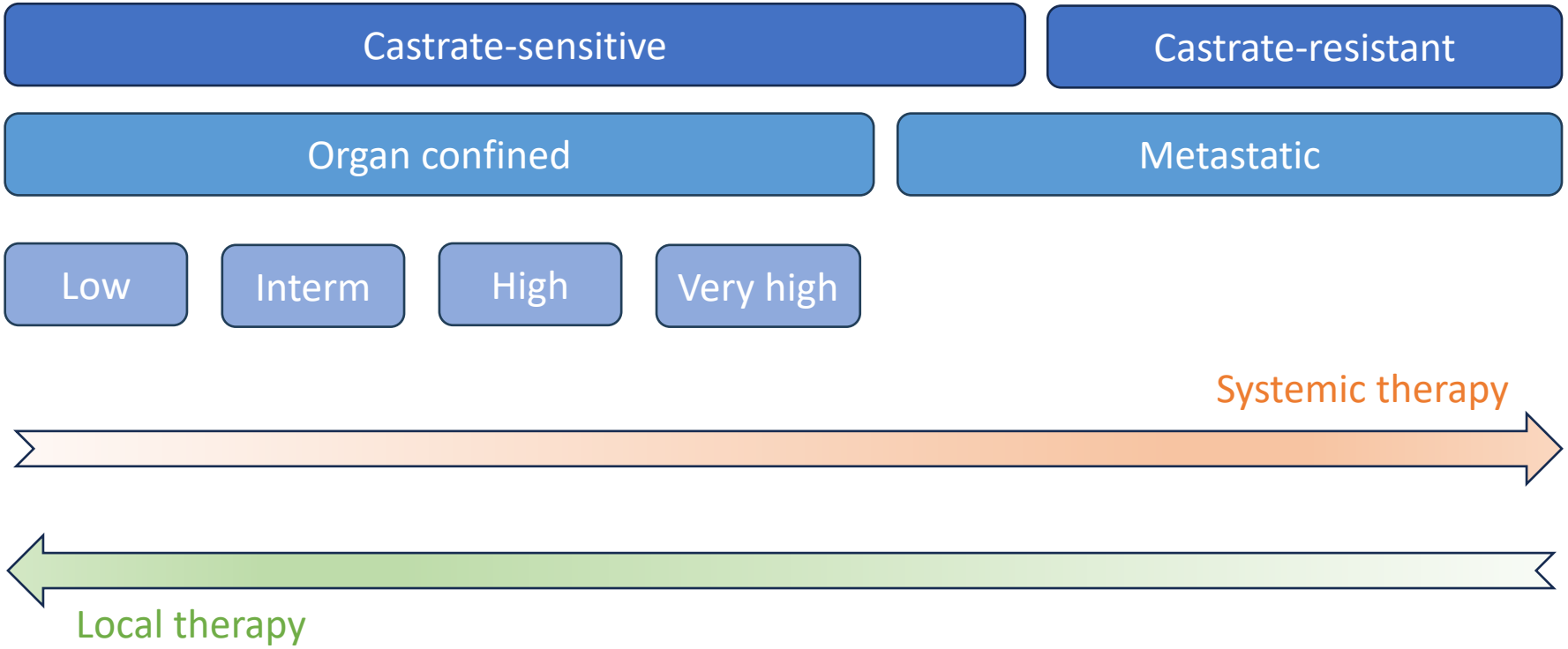
Definition			
Low-risk	**Intermediate-risk**	**High-risk**	
PSA < 10 ng/mL and GS < 7 (ISUP grade 1) and cT1-2a*	PSA 10–20 ng/mL or GS 7 (ISUP grade 2/3) or cT2b*	PSA > 20 ng/mL or GS > 7 (ISUP grade 4/5) or cT2c*	any PSA any GS (any ISUP grade) cT3-4* or cN+**
Localised			**Locally advanced**

GS = Gleason score; ISUP = International Society for Urological Pathology; PSA = prostate-specific antigen.

**** Based on digital rectal examination.***

***** Based on CT/bone scan.***

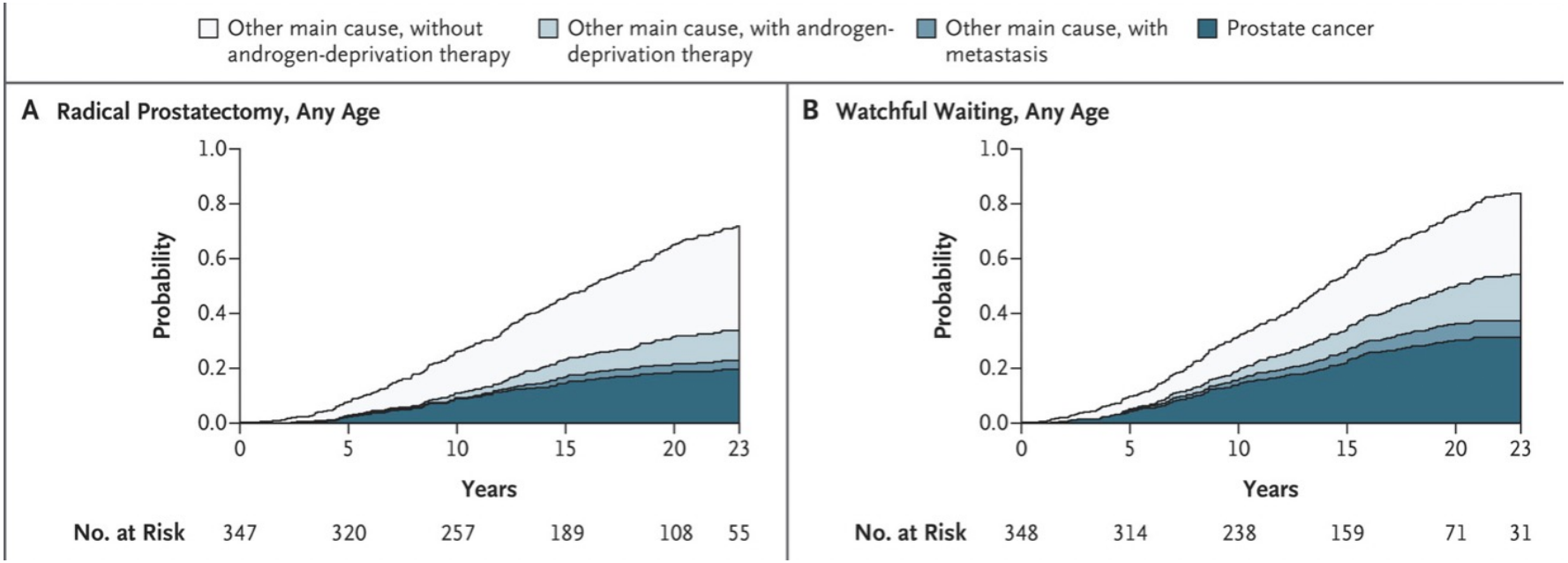
The prostate cancer disease spectrum



Surgery

The evidence.

Prospective evidence for surgery: SPGC-4



Bill-Axelson et al. 2018 NEJM

Which pts enrolled in SPGC-4?

- Median age 65 yo.
- Median PSA 13
- T1-T2 patients
- Pre-op: only up to 6% had Gleason 8-9
- Postop:
  - 35% R1
  - 47% T3a
  - 13% Gleason 8-9

So these patients were NOT really high risk or locally advanced.

Bad prognostic groups following RALP

Table 3. Univariate and Multivariate Cox Regression Analyses of Histopathological Risk Factors Based on Tumor Specimens from Radical Prostatectomy.

Death from prostate cancer				
Margins				
Negative	184	24	Reference	Reference
Positive	99	24	2.55 (1.42–4.56)	1.16 (0.62–2.15)
Extracapsular extension				
Absent	151	9	Reference	Reference
Present	132	38	7.61 (3.66–15.84)	5.21 (2.42–11.22)
Gleason score of prostatectomy specimen				
3–6	88	3	Reference	Reference
3+4	87	5	1.91 (0.46–7.99)	0.99 (0.23–4.33)
4+3	70	21	11.78 (3.51–39.55)	5.73 (1.59–20.67)
8 or 9	38	19	20.06 (5.93–67.91)	10.63 (3.03–37.30)

* The model was adjusted for age group (<65 vs. ≥65 years).
† The model was adjusted for age group (<65 vs. ≥65 years), PSA level, margins, capsular extension, and Gleason score.

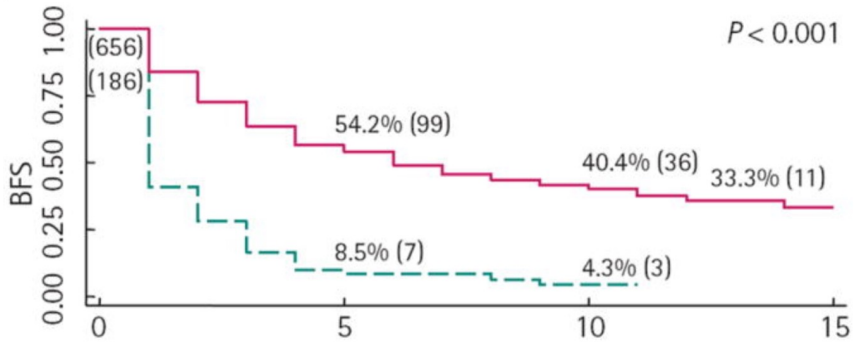
Who needs multimodal therapy?

Recommendations	Strength rating
Do not prescribe adjuvant androgen deprivation therapy (ADT) to pN0 patients.	Strong
In pN0 patients with ISUP grade group 4–5 and pT3 ± positive margins, offer adjuvant intensity-modulated radiation therapy (IMRT)/volumetric modulated arc therapy (VMAT) plus image-guided radiation therapy (IGRT).	Strong
In pN1 patients, after an extended lymph node dissection, discuss three management options, based on nodal involvement characteristics: 1. Offer adjuvant ADT; 2. Offer adjuvant ADT with additional IMRT/VMAT plus IGRT; 3. Offer observation (expectant management) to a patient after eLND and ≤ 2 nodes and a PSA < 0.1 ng/mL.	Weak

So in case we offer all grade group 4-5 AND pT3 patients postop RT, why do we even propose this strategy as we have no proof it is better that RT + ADT as primary treatment?

Who needs multimodal therapy?

- All patients with persisting or rising PSA following RP.
- Which patients have a higher chance of BCR in case of GI 8-10 at biopsy?
  - PSA concentration of > 10 ng/mL,
  - clinical stage ≥ T2b,
  - Gleason pattern 9 or 10 at biopsy,
  - increasing number of cores with high-grade cancer and
  - > 50% core involvement.

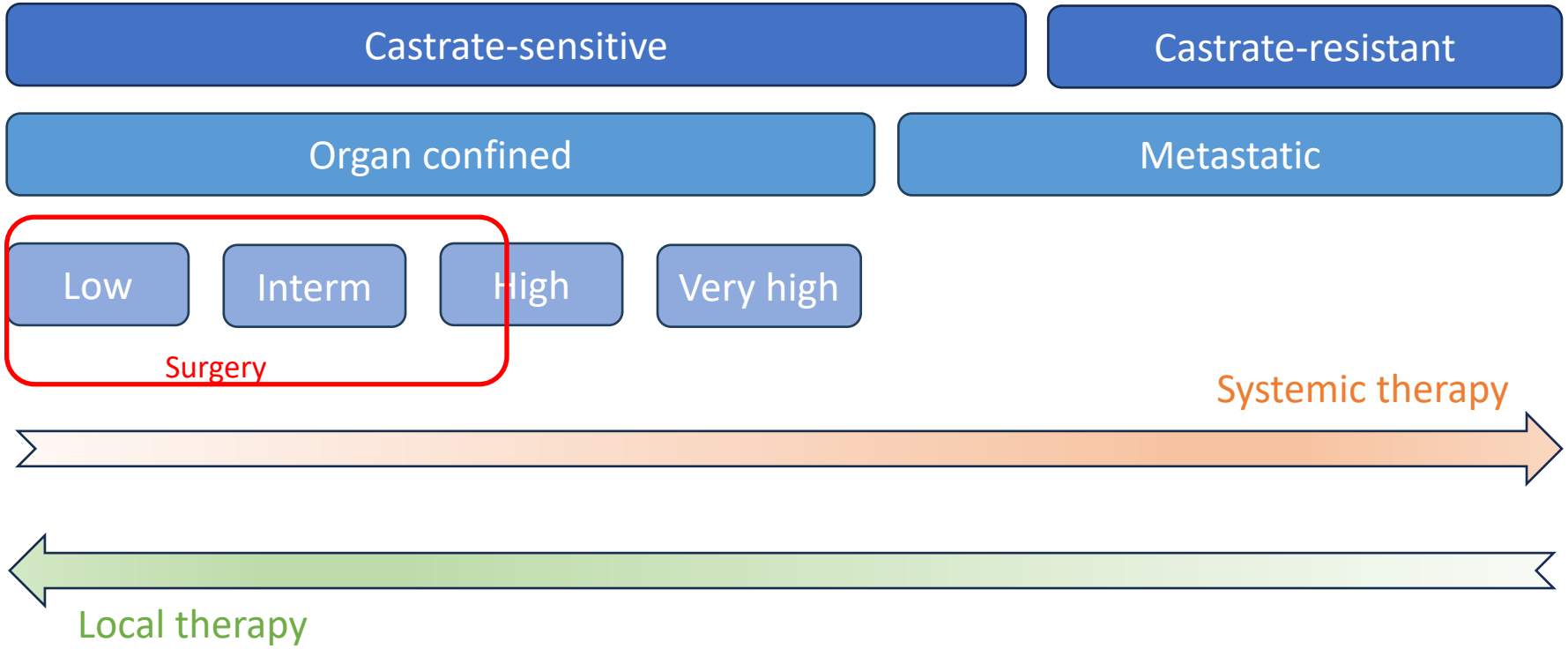


- >45% of the favorable pts require multimodal Tx
- >90% of the unfav require multimodal Tx

The Hierarchy of Evidence in Surgical Trials for High-Risk CaP

Strength rating = WEAK

The prostate cancer disease spectrum



Radiotherapy

The evidence.

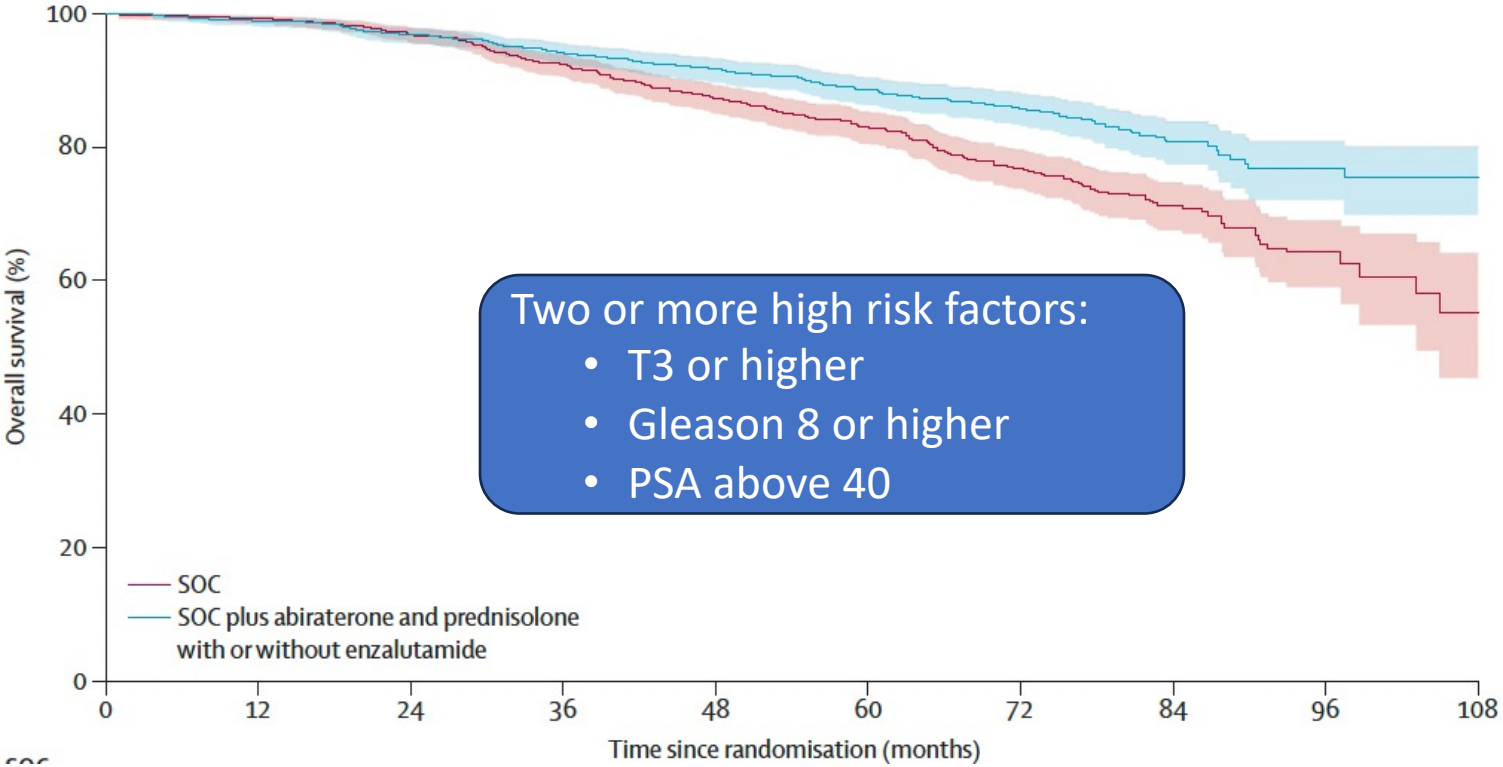
High risk/locally advanced PCa: multiple RCTs on benefit of RT+ADT

TABLE 2. Phase III Randomized Trials of ADT Use in Combination With Radiation Therapy for Localized Prostate Cancer

Trial	Year	Stage	No. of Patients	Arms	RT	Primary Endpoint	OS
RTOG 85-31[61]	2005	T3N0-1 (15% RP)	977	RT ± LHRHa/orchiectomy until progression	65–70 Gy		Improved survival (10-year survival 49% vs. 39%)
RTOG 86-10[62]	2008	T2-4N0-1	456	RT ± LHRHa + flutamide 2 months before and concurrent vs. no ADT	65–70 Gy	10–year OS	No difference (10-year OS 43% vs. 34%)
RTOG 92-02[63]	2008	T2c-4N0-1M0	1,554	LHRHa + flutamide × 4 months + RT ± 24-month adjuvant LHRHa	65–70 Gy	10–year DFS	Improved OS in Gleason 8–10 subgroup (45% vs. 32%)
EORTC 22961[64]	2009	T1c-2abN1M0 or T2c-4N0-1M0	970	LHRHa + antiandrogen × 6 months + RT ± 30-month adjuvant LHRHa	70 Gy	OS (noninferior)	Improved OS (5-year mortality 15% vs. 19%)
EORTC 22836[60]	2010	T1-2 WHO grade 3 or T3-4	415	RT ± LHRHa × 3 years	70 Gy	DFS	Improved OS (10-year OS 58% vs. 40%)
TROG 96-01[65]	2011	T2b-4N0M0	802	Neoadjuvant LHRHa + flutamide (0 vs. 3 vs. 6 months) + RT	66 Gy	Time to local failure; PCSM	Improved PCSM (10-year PCSM 11% vs. 22% for 6 mos vs. no ADT)
DART 01/05 GICOR[66]	2015	T1c-T3bN0M0	255	LHRHa + antiandrogen × 4 months + RT ± 24-month adjuvant LHRHa	76 Gy	BDFS	Improved OS (5-year OS 95% vs. 86%)
Nabid[67]	2018	T3-4 or PSA > 20 ng/mL or Gleason > 7	630	LHRHa + antiandrogen × 4 months + RT + 36- vs. 18-month adjuvant LHRHa	70 Gy	OS	No difference (5-year OS 91% vs. 86%)
TROG 03-04[68]	2019	T2b-N0M0 or T2a + PSA ≥ 10 ng/mL and Gleason ≥ 7	1,071	Neoadjuvant LHRHa × 6 months + RT ± 12-month adjuvant LHRHa ± 18-month zoledronic acid	66–74 Gy (or 46 Gy + HDB boost 19.5 Gy)	PCSM	Improved PCSM (10% vs. 13% for 18 vs. 6 months of ADT)

Abbreviations: ADT, androgen deprivation therapy; RT, radiation therapy; OS, overall survival; RP, radical prostatectomy; LHRHa, lutenizing hormone releasing hormone agonist; DFS, disease-free survival; PCSM, prostate cancer–specific mortality; BDFS, biochemical disease-free survival; PSA, prostate-specific antigen; HDB, high-dose brachytherapy boost.

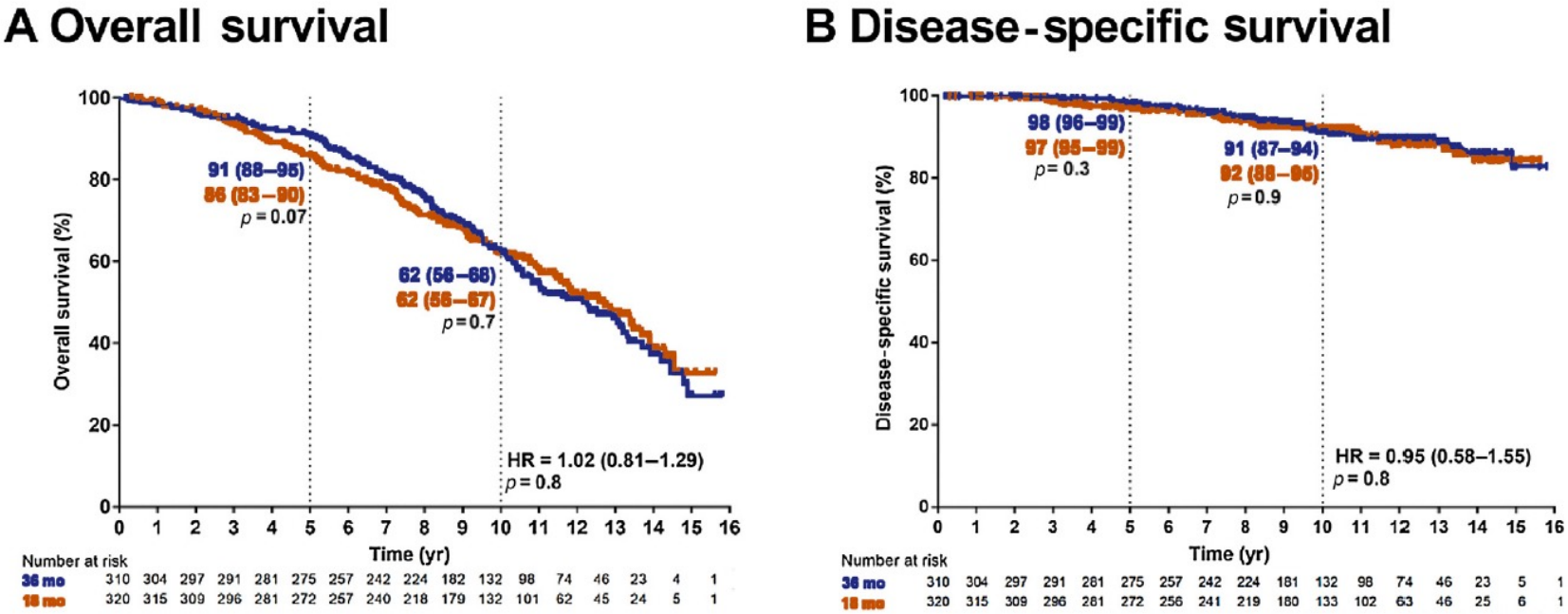
Systemic therapy intensification: ADT+ARTA



Two or more high risk factors:

- T3 or higher
- Gleason 8 or higher
- PSA above 40

Optimal duration of ADT? 18 – 24 – 36



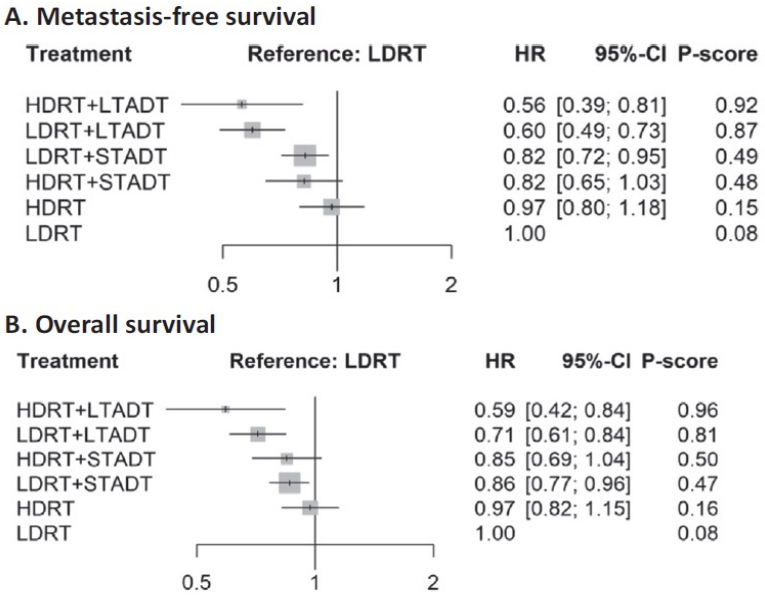
No evidence of 36 months of ADT being superior to 18 months

So it appears that there is a limit to the benefit of adding systemic therapy for unselected patients

Nabid et al. Eur Urol 2018

Radiotherapy OR systemic therapy intensification? HEAT

- <u>HEAT</u> (meta-analysis): Compare the relative benefits of RT dose escalation / ADT
- 11862 pts, 13 trials (45% IR / 45% HR)

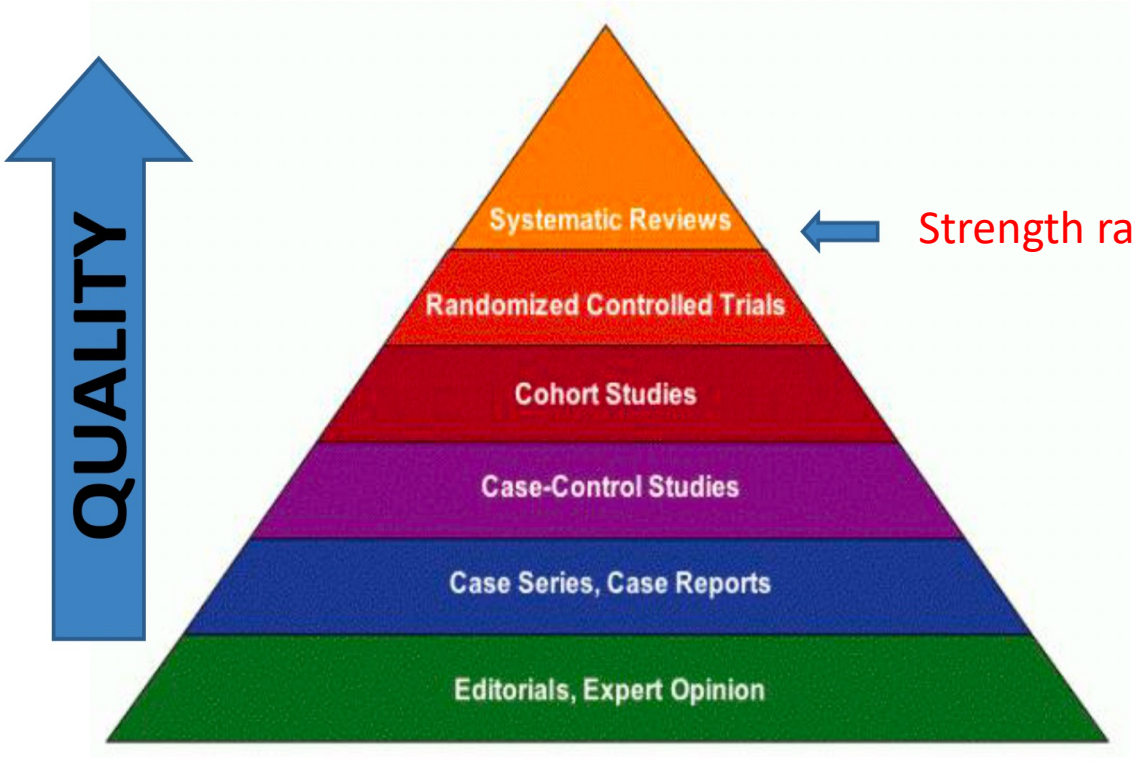


Duration of ADT influences MFS and OS, NOT RT dose.

So it appears that there is a limit to the benefit of “local” control!

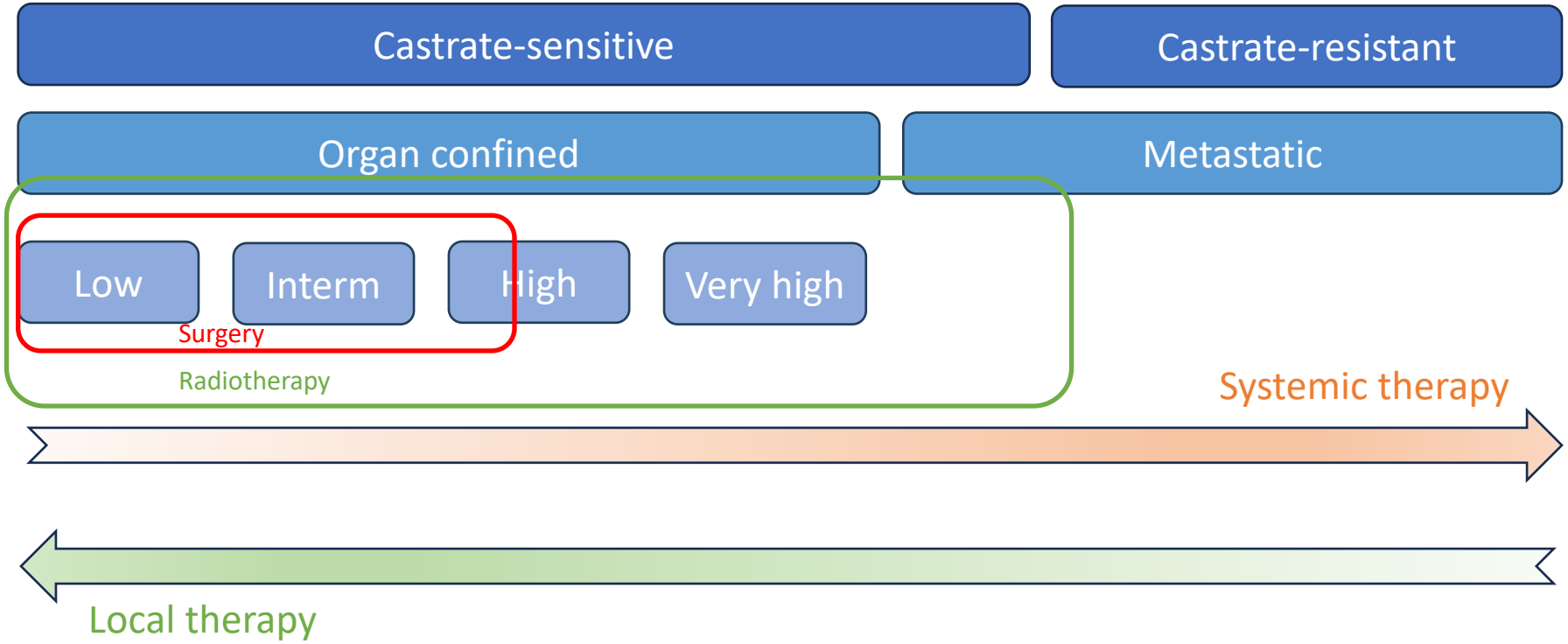
Kishan AU, Wang X, Sun Y, et al. High-dose Radiotherapy or Androgen Deprivation Therapy (HEAT) as Treatment Intensification for Localized Prostate Cancer: An Individual Patient-data Network Meta-analysis from the MARCAP Consortium. *Eur Urol*. 2022;82(1):106-114. doi:10.1016/j.eururo.2022.04.003

The Hierarchy of Evidence in Oncology for High-Risk Disease



Strength rating = STRONG

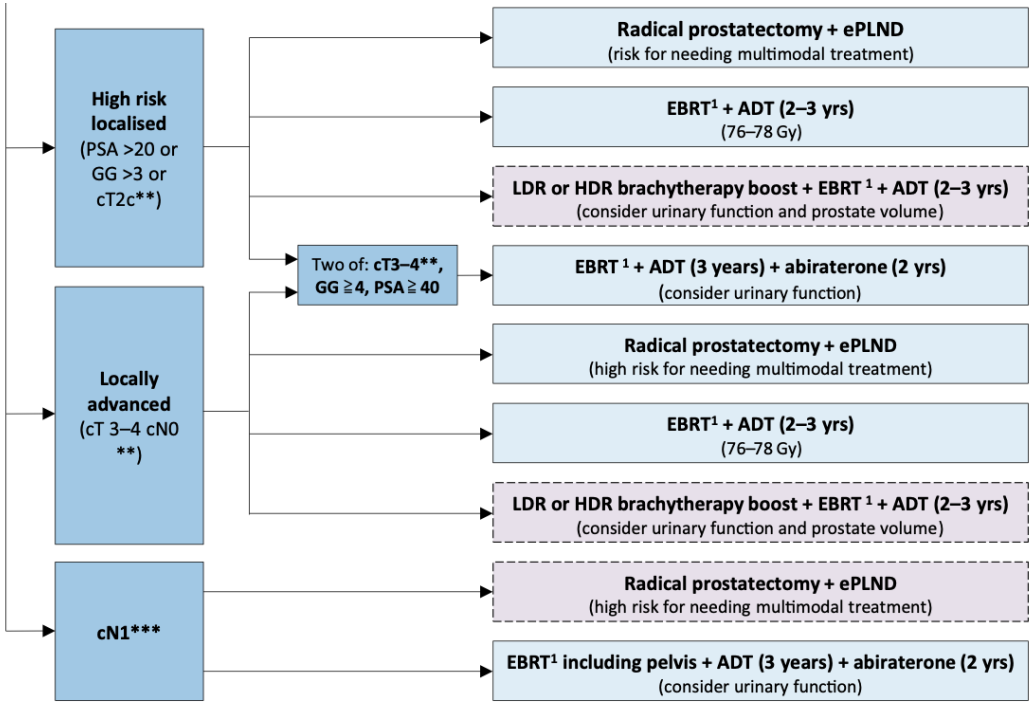
The prostate cancer disease spectrum



Conclusion

- Level 1 evidence for RT accross all risk groups
- Surgery has less evidence as compared to EBRT for high risk, no evidence for locally advanced or M1 disease
- There is NO evidence that multimodal therapy is better than primary EBRT + systemic Tx for locally advanced PCa.
- Some patients with high risk disease will need less treatment, some will need more => personalization.

EAU guidelines



Strength rating

strong

weak

strong

weak

weak

strong

The future is personalization?

A patient

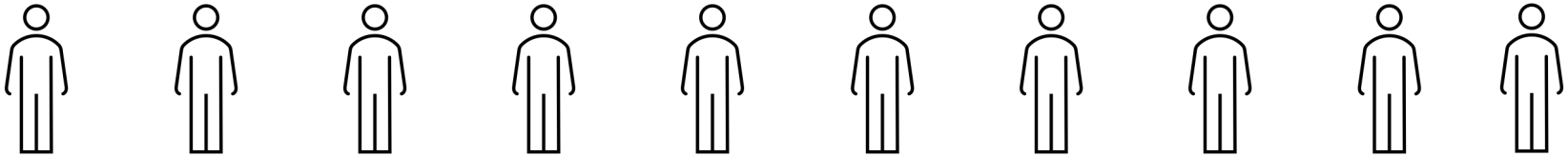
- 65 year old, good performance, no comorbidities
  - PSA 11
  - Gleason 9 at biopsy
  - cT3a on rectal examination (confirmed on MRI)
  - No nodal or distant metastases on imaging.

What is the chance a PSMA PET will show N1/M1 disease?
What is the optimal duration or type of systemic therapy?

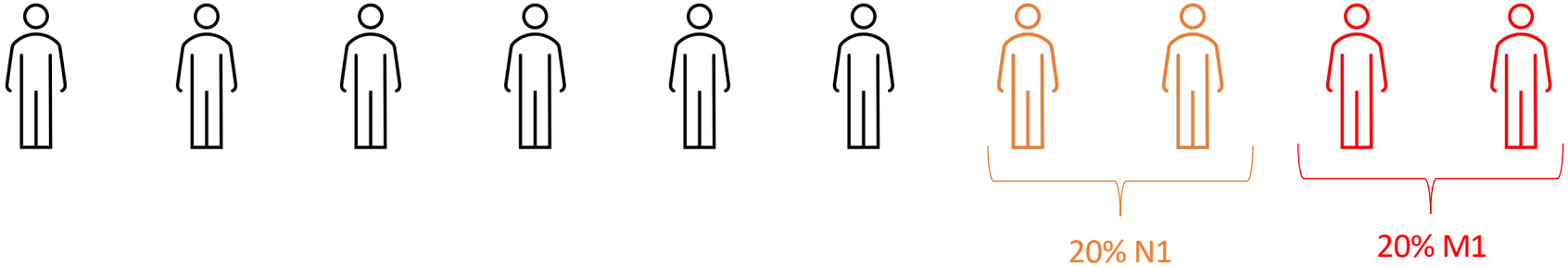
How could we personalize therapy?

Imaging impact

Conventional staging



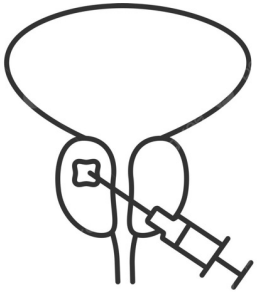
PSMA PET-CT



Do these patients require more therapy?

How could we personalize therapy?

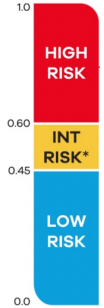
The future: genomic score



Highest biopsy score

RNA extraction and amplification

Whole transcriptome microarray

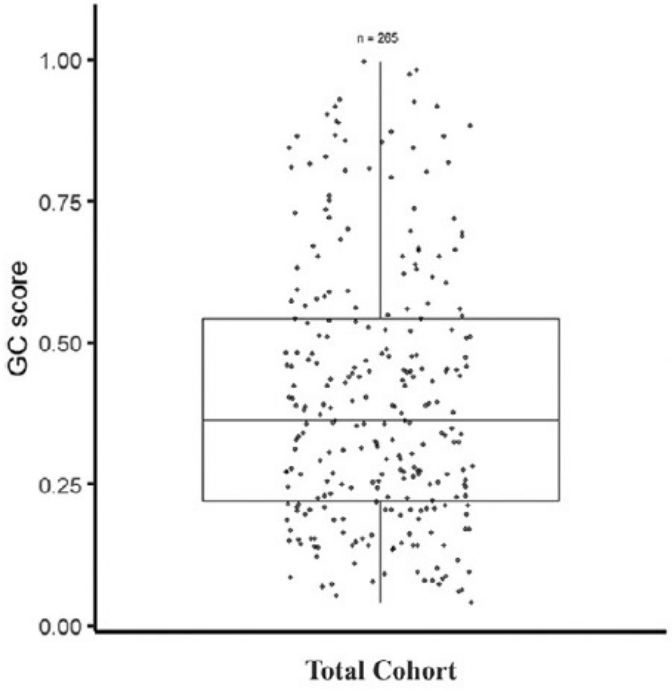


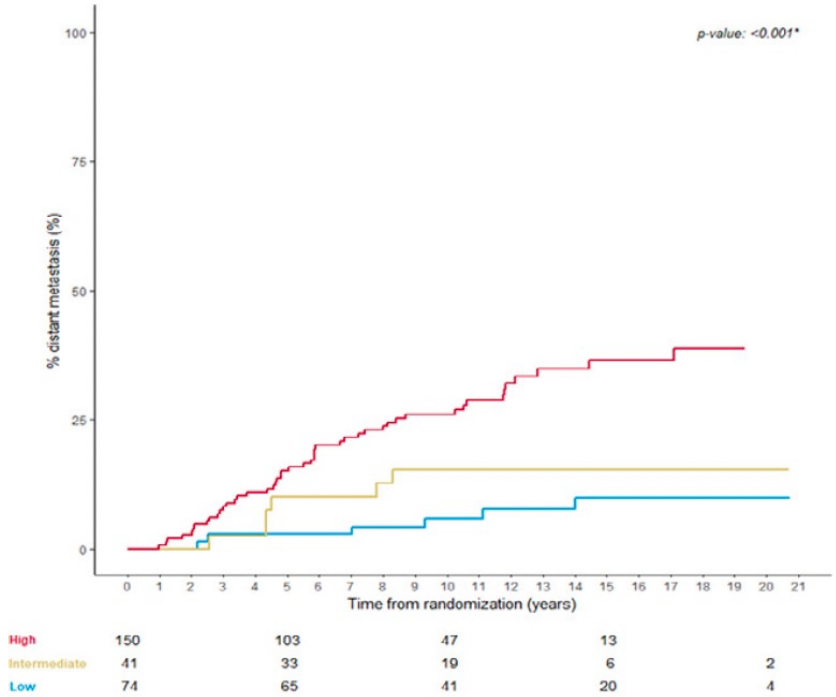
Decipher risk score

Hypothesis:

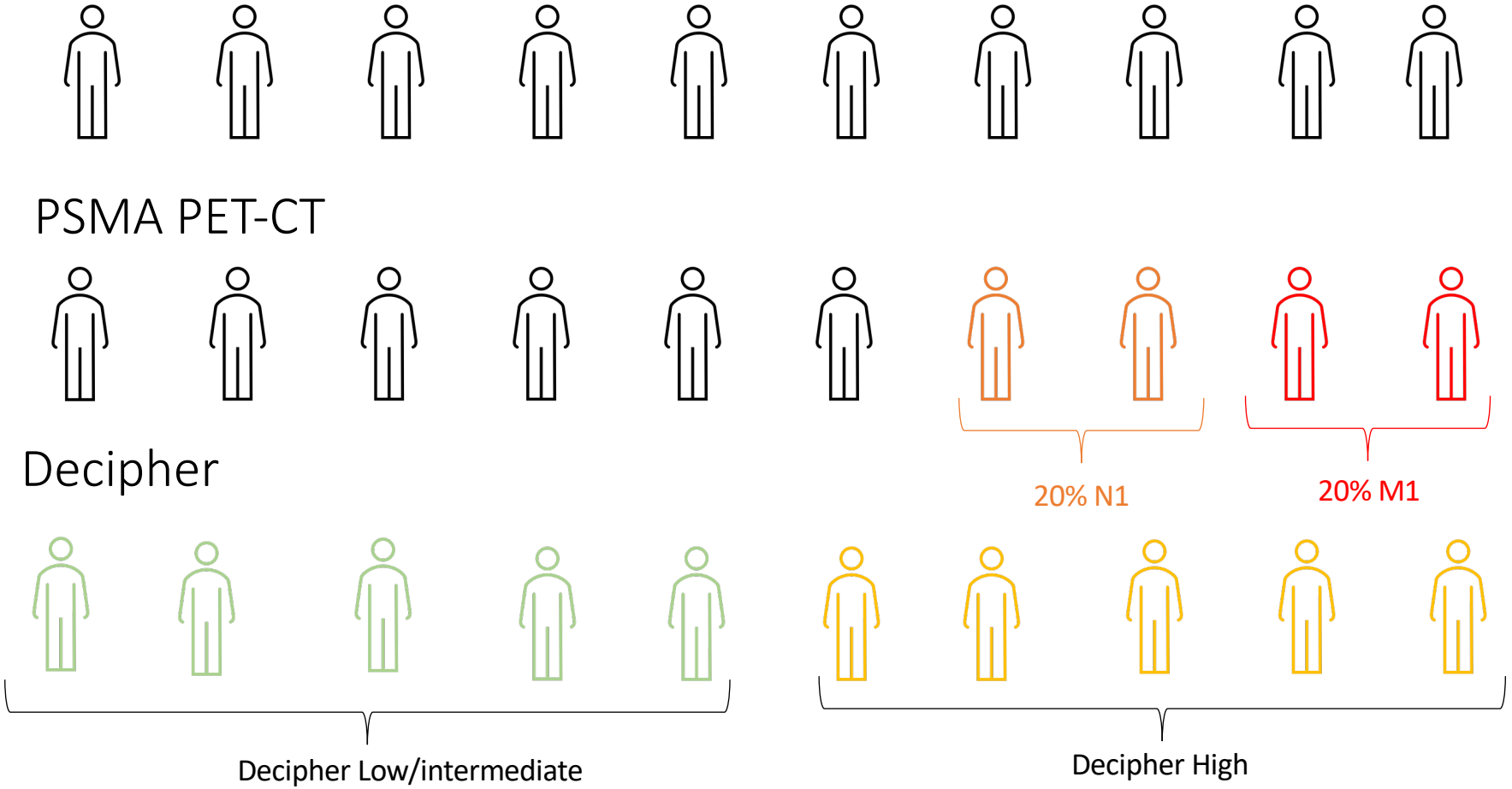
- Low GC score: no benefit from intensification
- High GC score: benefit from intensification

Analysis of a Biopsy-Based Genomic Classifier in High-Risk Prostate Cancer: Meta-Analysis of the NRG Oncology/RTOG 9202, 9413, and 9902 Phase 3 Randomized Trials

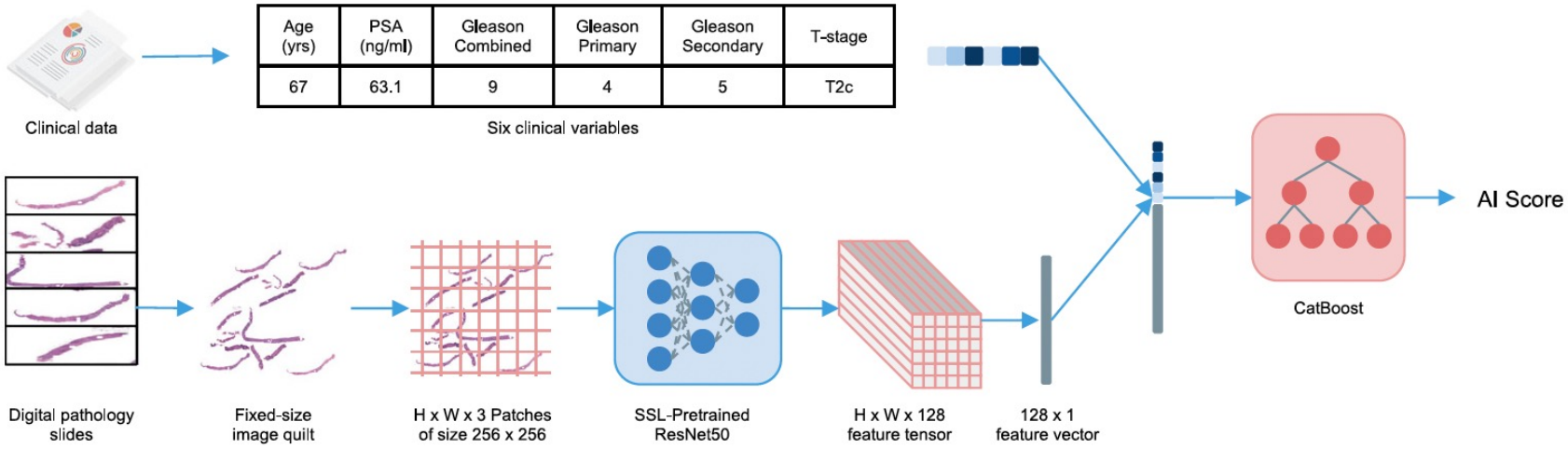




Conventional staging



The future: digital pathology



Hypothesis:

- Low AI score: no benefit from intensification
- High AI score: benefit from intensification

The future: Digital pathology

Primary Endpoint Results (DM)

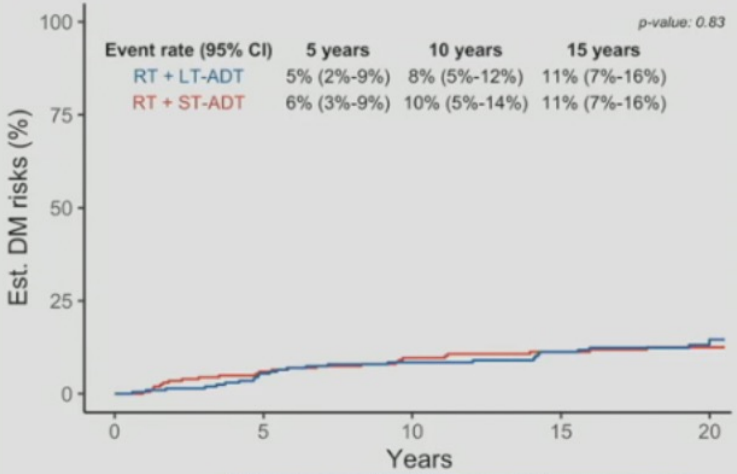
~⅓ of men with high-risk prostate cancer could safely avoid LT-ADT

254 men (21%) developed DM, and risk differed by AI Biomarker groups AND treatment

Biomarker Negative Group (n = 407)

p-value: 0.83

Event rate (95% CI)	5 years	10 years	15 years
RT + LT-ADT	5% (2%-9%)	8% (5%-12%)	11% (7%-16%)
RT + ST-ADT	6% (3%-9%)	10% (5%-14%)	11% (7%-16%)

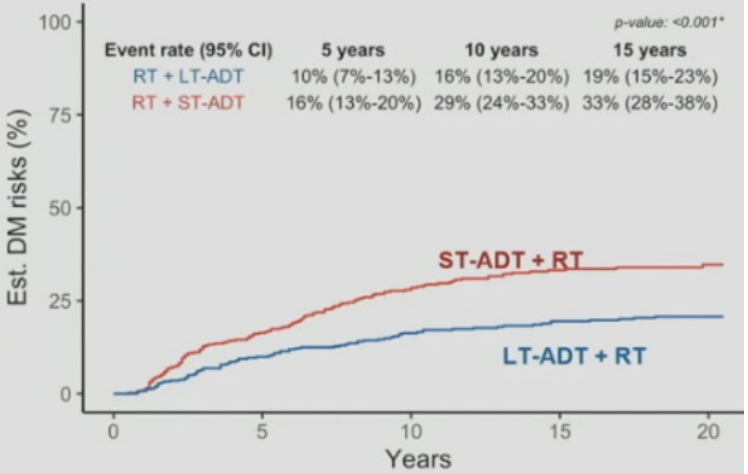


HR 1.06 (0.61 - 1.84), p = 0.84

Biomarker Positive Group (n = 785)

p-value: <0.001*

Event rate (95% CI)	5 years	10 years	15 years
RT + LT-ADT	10% (7%-13%)	16% (13%-20%)	19% (15%-23%)
RT + ST-ADT	16% (13%-20%)	29% (24%-33%)	33% (28%-38%)

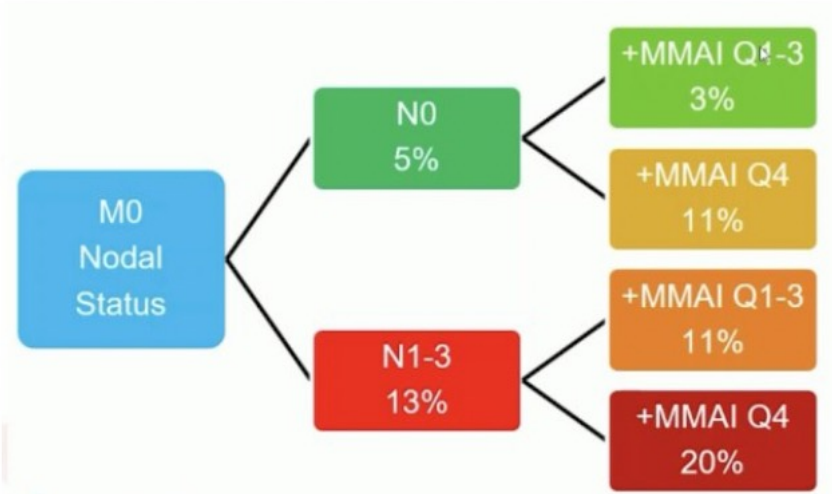


HR 0.55 (0.41 - 0.73), p < 0.001

NRG ONCOLOGY™

Presented by: Andrew J. Armstrong, MD, Professor, Department of Medicine, Duke Cancer Institute Center for Prostate and Urologic Cancer, Duke University, Durham, NC

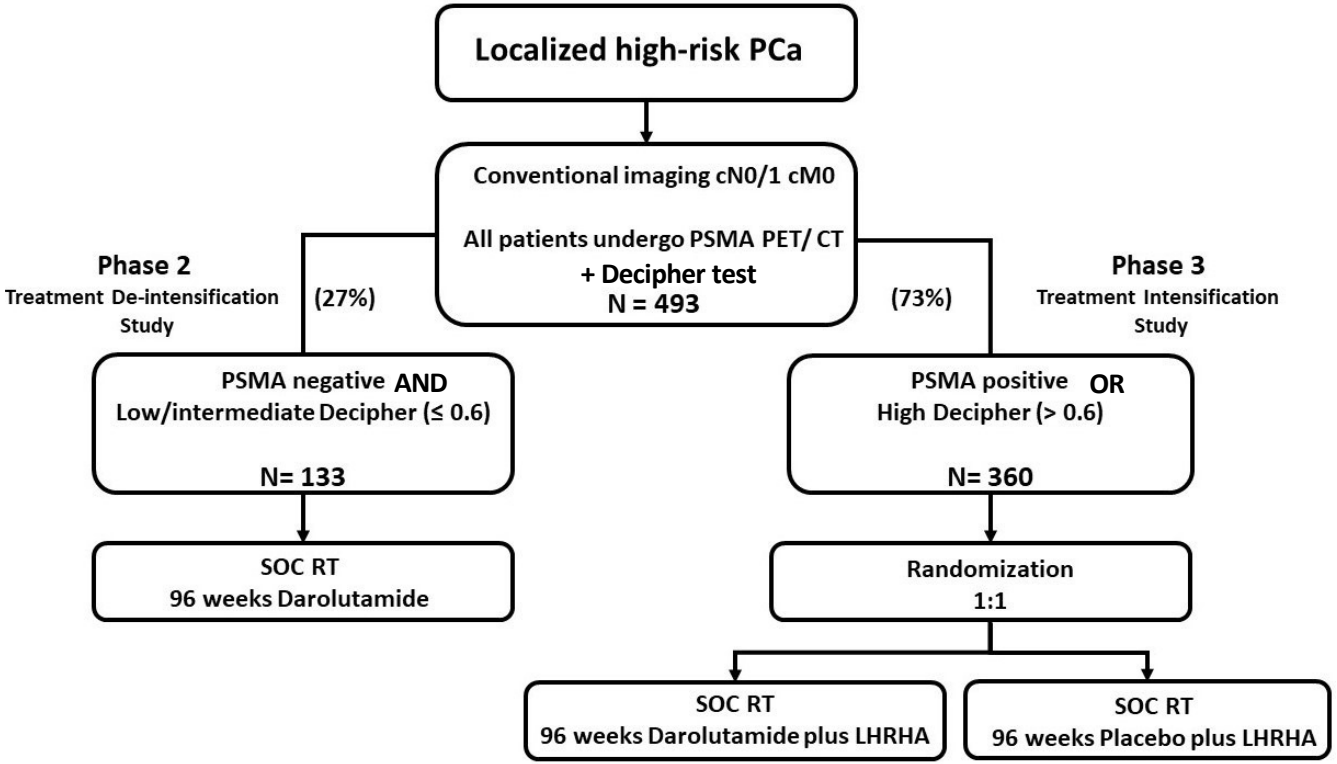
Digital pathology: ADT +...



MMAI model further stratifies very high risk patients.

C. Parker ESMO 23

Thunder trial design



- SOC RT includes radiotherapy of the prostate + pelvis and all visibile lesions on PSMA PET-CT (max 5 M1 lesions)
- In case >5 M1 lesions are detected on PSMA, docetaxel is allowed in both arms.