Disclosure of Conflicts of Interest

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- Industry
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  - Consulting: Optum Health

- Research funding
  - NCI
  - Movember Foundation

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Clinically Localized Prostate Cancer AUA/ASTRO Guideline 2022

Daniel A. Barocas, MD, MPH

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Acknowledgements

Eastham JA, et al. J Urol 2022
https://www.auanet.org/guidelines/guidelines/clinically-localized-prostate-cancer-aua/astro-guideline-2022
Cited throughout this talk

PANEL FORMATION AND SYSTEMATIC REVIEW

- This Guideline was produced by a multidisciplinary panel with representation from AUA, ASCO, ASTRO, and SUO as well as a patient advocate.

- Systematic Review Search Dates
  - Ovid MEDLINE (September 2021)
  - Cochrane Central Register of Controlled Trials (August 2021)
  - Cochrane Database of Systematic Reviews (September 2021)

- Evidence Base
  - 10,867 total citations reviewed
  - 221 articles included in discussion of 12 key questions

AUA EVIDENCE RATING SYSTEM

AUA Strength of Evidence Category	GRADE Certainty Rating	Definition
A	High	• We are very confident that the true effect lies close to that of the estimate of the effect
B	Moderate	• We are moderately confident in the effect estimate • The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
C	Low	• Our confidence in the effect estimate is limited • The true effect may be substantially different from the estimate of the effect
	Very Low	• We have very little confidence in the effect estimate • The true effect is likely to be substantially different from the estimate of effect

	Evidence Strength A (High Certainty)	Evidence Strength B (Moderate Certainty)	Evidence Strength C (Low Certainty)
Strong Recommendation (Net benefit or harm substantial)	Benefits > Risks/Burdens (or vice versa) Net benefit (or net harm) is substantial Applies to most patients in most circumstances and future research unlikely to change confidence	Benefits > Risks/Burdens (or vice versa) Net benefit (or net harm) is substantial Applies to most patients in most circumstances but better evidence could change confidence	Benefits > Risks/Burdens (or vice versa) Net benefit (or net harm) appears substantial Applies to most patients in most circumstances but better evidence is likely to change confidence (rarely used to support a Strong Recommendation)
Moderate Recommendation (Net benefit or harm moderate)	Benefits > Risks/Burdens (or vice versa) Net benefit (or net harm) is moderate Applies to most patients in most circumstances and future research is unlikely to change confidence	Benefits > Risks/Burdens (or vice versa) Net benefit (or net harm) is moderate Applies to most patients in most circumstances but better evidence could change confidence	Benefits > Risks/Burdens (or vice versa) Net benefit (or net harm) appears moderate Applies to most patients in most circumstances but better evidence is likely to change confidence
Conditional Recommendation (No apparent net benefit or harm)	Benefits = Risks/Burdens Best action depends on individual patient circumstances Future research unlikely to change confidence	Benefits = Risks/Burdens Best action appears to depend on individual patient circumstances Better evidence could change confidence	Balance between Benefits & Risks/Burdens unclear Alternative strategies may be equally reasonable Better evidence likely to change confidence
Clinical Principle	A statement about a component of clinical care that is widely agreed upon by urologists or other clinicians for which there may or may not be evidence in the medical literature		
Expert Opinion	A statement, achieved by consensus of the Panel, that is based on members clinical training, experience, knowledge, and judgment for which there may or may not be evidence in the medical literature		

RISK ASSESSMENT

1. Clinicians <u>should</u> use **clinical T stage, serum prostate-specific antigen (PSA), Grade Group (Gleason score), and tumor volume** on biopsy to risk stratify patients with newly diagnosed prostate cancer. (Strong Recommendation; Evidence Level: Grade A)

2. Clinicians <u>may</u> **selectively use tissue-based genomic biomarkers** when added risk stratification may alter clinical decision-making. (Expert Opinion)

3. Clinicians <u>should not</u> **routinely use tissue-based genomic biomarkers** for risk stratification or clinical decision-making. (Moderate Recommendation; Evidence Level: Grade B)

RISK GROUP CLASSIFICATION

Low-Risk	PSA <10 ng/mL AND Grade Group 1 AND clinical stage T1-T2a
Intermediate-Risk	PSA 10-<20 ng/mL OR Grade Group 2-3 OR clinical stage T2b-c
	· Favorable: Grade Group 1 with PSA 10-<20 ng/mL or clinical stage T2b-c and <50%* biopsy cores positive OR Grade Group 2 with PSA<10 ng/mL and clinical stage T1-2a and <50% biopsy cores positive
	· Unfavorable: Grade Group 1 with PSA 10-<20 ng/mL and clinical stage T2b-c OR Grade Group 2 with PSA 10-<20 ng/mL and/or clinical stage T2b-c and/or ≥50%* biopsy cores positive OR Grade Group 3 with PSA <20 ng/mL
High-Risk	PSA ≥20 ng/mL OR Grade Group 4-5 OR clinical stage T3

*Percent biopsy cores positive is the total number of cores containing cancer divided by total number of cores obtained x 100. This is not the percentage of cancer within a positive core. Regarding assessment of the percent biopsy cores positive for risk stratification, the Panel acknowledges that with the increasing use of pre-biopsy magnetic resonance imaging (MRI) and subsequent targeted biopsies, multiple cores may be obtained from a targeted lesion. Multiple cores from the same lesion should be considered as a single core (i.e., for the calculation of percentage cores positive in risk assessment). If all cores are negative, that is considered a single negative core. If one or more cores from the same lesion is positive, that is considered a single positive core, with the highest Gleason score used for risk stratification.

MISSING LINKS: Not included, but potentially important

- **Imaging to assign T stage**
  - T stage based on DRE, but MRI may provide additional information

- **PSA density**
  - PSA density $\geq$ 0.15 is associated with upgrading in men on active surveillance

- **Histologic variants**
  - Cribriform and intraductal patterns are associated with worse prognosis

- **Tissue-based genomic biomarkers**
  - Not recommended for routine use, but may be useful in selected situations in which added risk stratification may influence shared decision making

GERMLINE TESTING

4. Clinicians <u>should</u> perform an **assessment of patient and tumor risk factors to guide the decision to offer germline testing** that includes mutations known to be associated with aggressive prostate cancer and/or known to have implications for treatment. (Expert Opinion)

Strong family history of prostate cancer	Examples: first-degree relative or multiple second-degree relatives diagnosed with Grade Group 2 or higher prostate cancer, particularly at early age (< 60 years), particularly if metastatic or lethal
Strong personal or family history of related cancers	Examples: breast, colorectal, ovarian, pancreatic, upper tract urothelial carcinoma
Known family history of familial cancer risk mutation	Examples: BRCA1, BRCA2, ATM, Lynch-syndrome associated genes
Ashkenazi Jewish ancestry	Particularly in patients with Grade Group 2 or higher disease
Adverse tumor characteristics	Examples: High-risk disease; intermediate-risk disease with intraductal or cribriform morphology
*The Panel recognizes that this list is not exhaustive.	

Implementation of Germline Testing for Prostate Cancer: Philadelphia Prostate Cancer Consensus Conference 2019

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STAGING

5. Clinicians <u>should not</u> **routinely perform abdomino-pelvic computed tomography (CT) scan or bone scan in asymptomatic patients with low- or intermediate-risk prostate cancer**. (Expert Opinion)

6. Clinicians <u>should</u> **obtain a bone scan and either pelvic multi-parametric magnetic resonance imaging (mpMRI) or CT scan for patients with high-risk prostate cancer**. (Strong Recommendation; Evidence Level: Grade B)

   May consider in unfavorable intermediate risk

7. Clinicians <u>may</u> **obtain molecular imaging to evaluate for metastases in patients with prostate cancer at high risk for metastatic disease with negative conventional imaging**. (Expert Opinion)

RISK-BASED MANAGEMENT

SHARED DECISION-MAKING

8. Clinicians should inform patients that all prostate cancer treatments carry risk. The risks of treatment, in particular to patients' urinary, sexual, and bowel function, must be incorporated with the risk posed by the cancer, patient life expectancy, comorbidities, pre-existing medical conditions, and patient preferences to facilitate a shared decision-making approach to management. (Clinical Principle)

COMPONENTS OF SHARED DECISION-MAKING

The selection of a management strategy is preference-sensitive and very often based on patients' interpretation of the balance between treatment-specific risks and benefits.

Informing patients about the severity of their cancer (risk level)*
Assessing patients' relevant comorbidities and life expectancy**
Informing patients about the likelihood of cure, recurrence, and other oncologic endpoints of each management strategy/ treatment option (ideally using a risk calculator or nomogram)
Assessing patients' baseline disease-specific function (e.g., urinary, sexual, and bowel function) and the value or utility they place on each (ideally using standardized instruments, with or without decision aids)
Informing patients about their likelihood of specific short- and long-term side effects of each management strategy/ treatment option
*see Risk Stratification Table and associated text
** An accurate determination of a man's life expectancy based on age and comorbidities is difficult. Methods available to determine life expectancy include clinician prediction, model prediction, and publicly available calculators (e.g., https://www.ssa.gov/OACT/ population/longevity.html). Life expectancy may be assessed in conjunction with a patient's primary care physician.

ASSESSING LIFE EXPECTANCY

- Consideration of age and relevant comorbidities is essential.

- Family history and consultation with PCP may also be valuable.

Exact age	Male		
	Death probability [a]	Number of lives [b]	Life expectancy
69	0.020829	74,475	15.28
70	0.022364	72,924	14.60
71	0.024169	71,293	13.92
72	0.026249	69,570	13.25
73	0.028642	67,744	12.59
74	0.031380	65,804	11.95
75	0.034593	63,739	11.32
76	0.038235	61,534	10.71
77	0.042159	59,181	10.12
78	0.046336	56,686	9.54
79	0.050917	54,059	8.98

15 →

10 →

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ONCOLOGIC ENDPOINTS
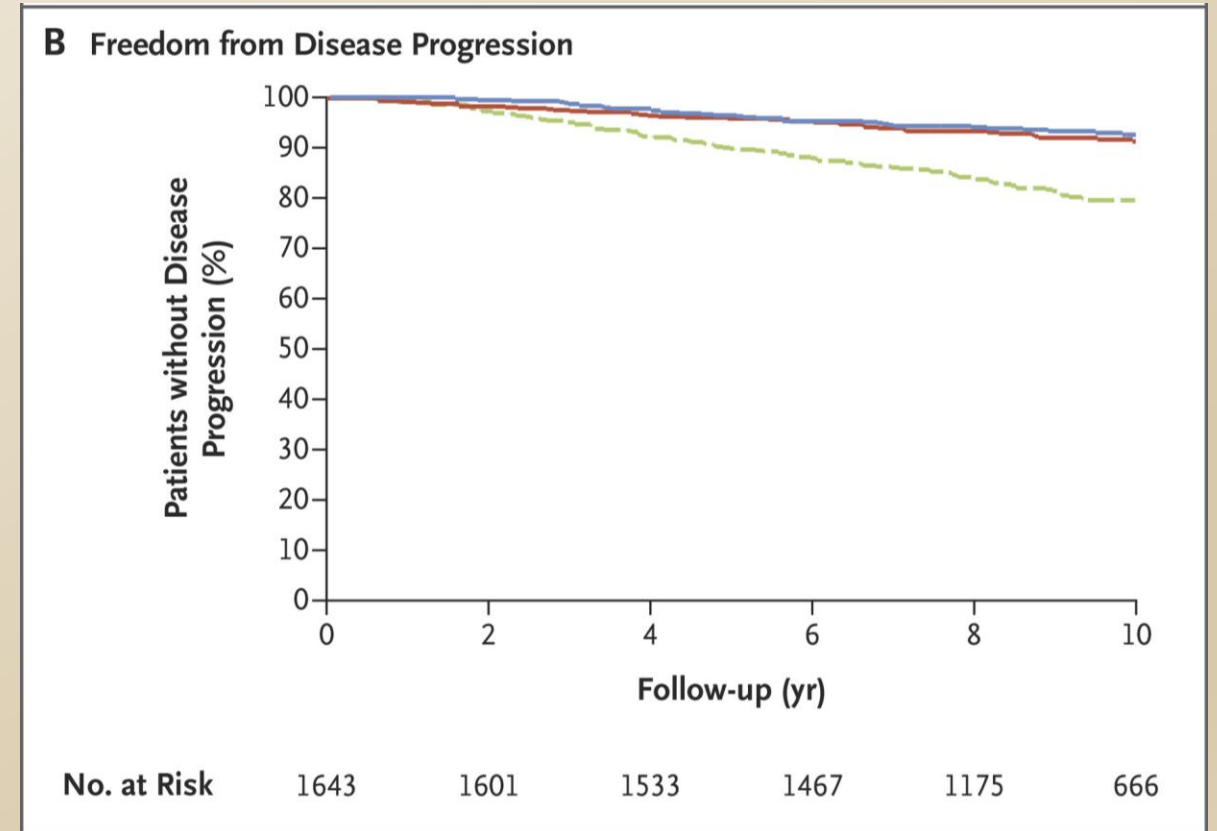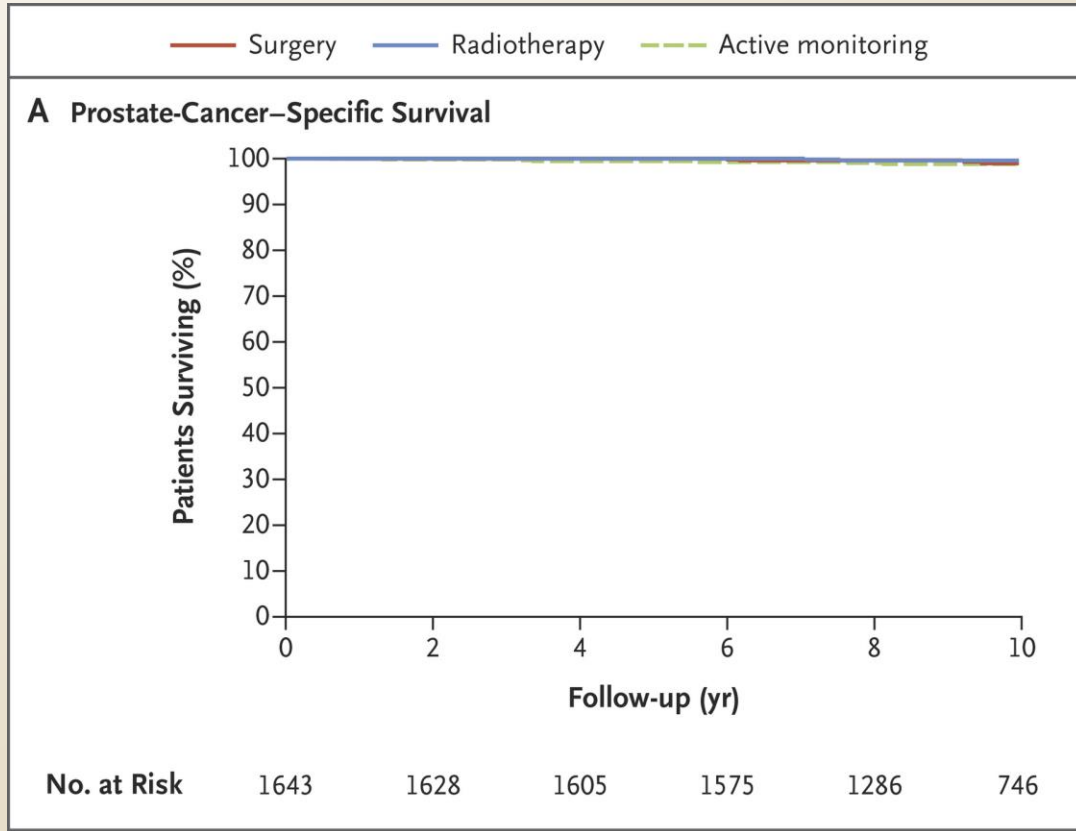
ProtecT, Hamdy et al. N Engl J Med 2016

Table 1. Prostate-Cancer Mortality, Incidence of Clinical Progression and Metastatic Disease, and All-Cause Mortality, According to Randomized Treatment Group.

Variable	Active Monitoring (N=545)	Surgery (N=553)	Radiotherapy (N=545)	P Value*
Prostate-cancer mortality				
Total person-yr in follow-up	5393	5422	5339	
No. of deaths due to prostate cancer†	8	5	4	
Prostate-cancer–specific survival — % (95% CI)†				
At 5 yr	99.4 (98.3–99.8)	100	100	
At 10 yr	98.8 (97.4–99.5)	99.0 (97.2–99.6)	99.6 (98.4–99.9)	
Prostate-cancer deaths per 1000 person-yr (95% CI)†	1.5 (0.7–3.0)	0.9 (0.4–2.2)	0.7 (0.3–2.0)	0.48
Incidence of clinical progression‡				
Person-yr of follow-up free of clinical progression	4893	5174	5138	
No. of men with clinical progression	112	46	46	
Clinical progression per 1000 person-yr (95% CI)	22.9 (19.0–27.5)	8.9 (6.7–11.9)	9.0 (6.7–12.0)	<0.001
Incidence of metastatic disease				
Person-yr of follow-up free of metastatic disease	5268	5377	5286	
No. of men with metastatic disease	33	13	16	
Metastatic disease per 1000 person-yr (95% CI)	6.3 (4.5–8.8)	2.4 (1.4–4.2)	3.0 (1.9–4.9)	0.004
All-cause mortality				
Total person-yr in follow-up	5393	5422	5339	
No. of deaths due to any cause	59	55	55	
All-cause deaths per 1000 person-yr (95% CI)	10.9 (8.5–14.1)	10.1 (7.8–13.2)	10.3 (7.9–13.4)	0.87

ProtecT, Hamdy et al. N Engl J Med 2016

ONCOLOGIC ENDPOINTS

https://www.mskcc.org/nomograms/prostate/pre_op

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Pre-Radical Prostatectomy

Your Results

Edit Information

Click the +/- to read more about your results

Primary Treatment Outcomes

+ PROBABILITY OF CANCER-SPECIFIC SURVIVAL AFTER RADICAL PROSTATECTOMY — 10 YR **99**% 15 YR **99**%

+ PROGRESSION-FREE PROBABILITY AFTER RADICAL PROSTATECTOMY — 5 YR **69**% 10 YR **55**%

Extent of Disease Probability

Each extent-of-disease probability percentage is an independent prediction. We therefore would not expect these percentages to equal 100.

+ ORGAN-CONFINED DISEASE — **41**%

+ EXTRACAPSULAR EXTENSION — **55**%

+ LYMPH NODE INVOLVEMENT — **9**%

+ SEMINAL VESICLE INVASION — **6**%

ASSESSING BASELINE URINARY, SEXUAL AND BOWEL FUNCTION

- Baseline function is one of the strongest predictors of functional outcomes

- The clinician should ascertain the patient's pre-treatment urinary, bowel, and sexual function (and hormone therapy-related domains if concurrent hormone therapy and radiation is being considered), preferable with a standardized instrument.
 - The Expanded Prostate Cancer Index Composite (EPIC)-26

Side Effects of Treatment in Men with Low- and Favorable-intermediate Risk Disease

JAMA | Original Investigation

Patient-Reported Outcomes Through 5 Years for Active Surveillance, Surgery, Brachytherapy, or External Beam Radiation With or Without Androgen Deprivation Therapy for Localized Prostate Cancer

Karen E. Hoffman, MD, MHSc, MPH; David F. Penson, MD, MPH; Zhiguo Zhao, MS; Li-Ching Huang, PhD; Ralph Conwill, BS; Aaron A. Laviana, MD; Daniel D. Joyce, MD; Amy N. Luckenbaugh, MD; Michael Goodman, MD, MPH; Ann S. Hamilton, PhD, MA; Xiao-Cheng Wu, MD, MPH; Lisa E. Paddock, PhD, MPH; Antoinette Stroup, PhD; Matthew R. Cooperberg, MD, MPH; Mia Hashibe, PhD; Brock B. O'Neil, MD; Sherrie H. Kaplan, PhD, MS, MPH; Sheldon Greenfield, MD; Tatsuki Koyama, PhD; Daniel A. Barocas, MD, MPH
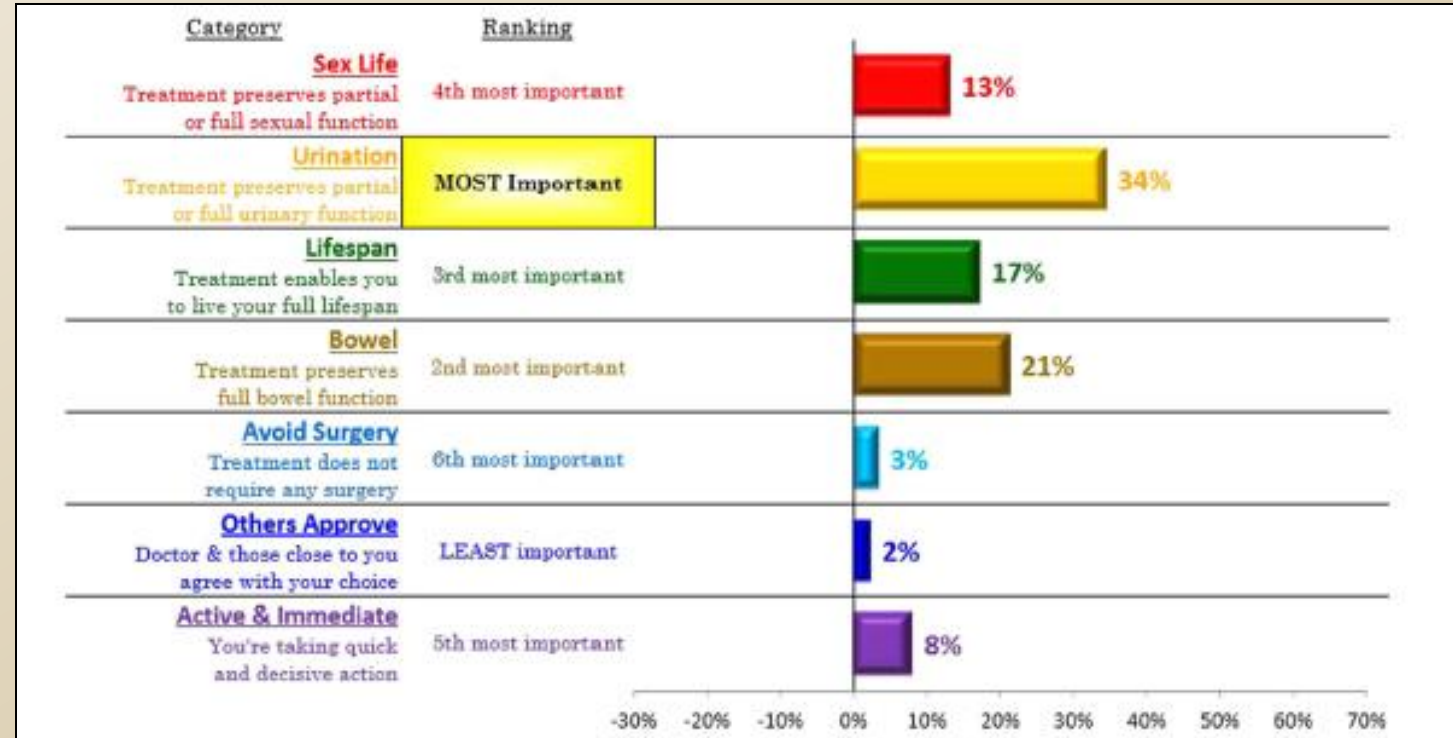
Hoffman K et al. JAMA, 2020.
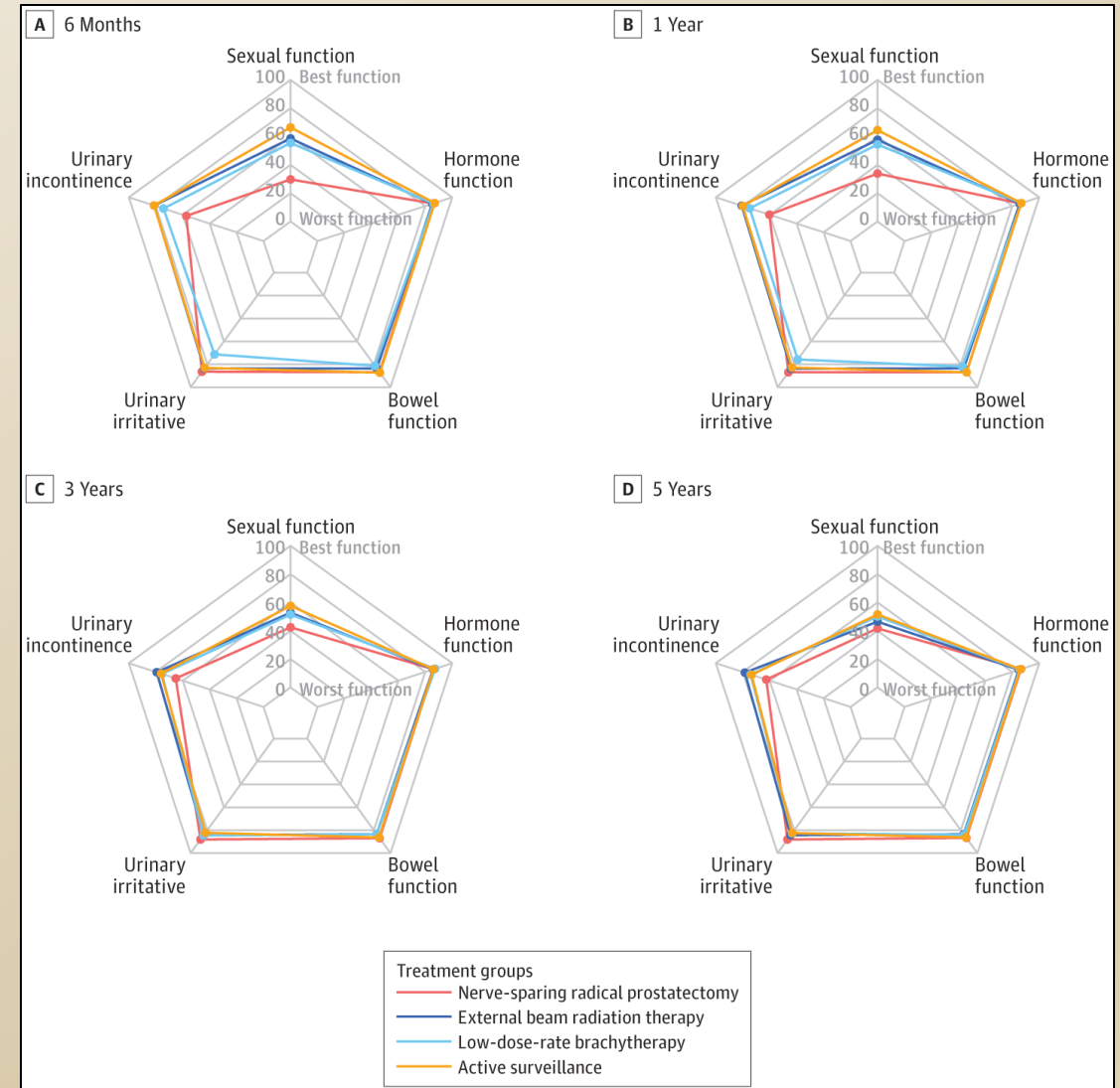
Patient References and Priorities

Does Patient Preference Measurement in Decision Aids Improve Decisional Conflict? A Randomized Trial in Men with Prostate Cancer

Joseph D. Shirk[1] · Catherine M. Crespi[2] · Josemanuel D. Saucedo[1] · Sylvia Lambrechts[1] · Ely Dahan[3] · Robert Kaplan[4] · Christopher Saigal[1]

Shirk JD et al. Patient, 2017.

RISK-BASED MANAGEMENT

10. For patients with **low-risk** prostate cancer, clinicians <u>should</u> **recommend active surveillance as the preferred management option**. (Strong Recommendation; Evidence Level: Grade A)

Briganti A, et al. Euro Urol, 2018

Studies	N	Median follow-up (yr)	Overall survival	Cancer-specific survival	Reclassification rate	Curative intervention rate
Goteborg [Godtman Eur Urol 2016]	474	8.0 yr	10 yr: 80% 15 yr: 51%	10 yr: 99.5% 15 yr: 96.0%	–	10 yr: 53% 15 yr: 66%
John Hopkins [Tosoian JCO 2015]	1298	5.0 yr	10 yr: 93% 15 yr: 69%	10 yr: 99.9% 15 yr: 99.9%	10 yr: 26% 15 yr: 31%	10 yr: 50% 15 yr: 57%
Miami [Soloway Eur Urol 2010]	230	3.6 yr	–	3 yr: 100%	–	33 mo: 14%
MSKCC [Adamy J Urol 2011]	238	1.8 yr	NR	NR	2 yr: 20% 5 yr: 40%	–
PRIAS [Bokhorst Eur Urol 2016]	5302	NR	5 yr: 97% 10 yr: 89%	5 yr: >99% 10 yr: >99%	5 yr: 34% 10 yr: 41%	5 yr: 52% 10 yr: 73%
Royal Marsden [Selvadurai Eur Urol 2013]	471	5.7 yr	8 yr: 91%	8 yr: 98%	5 yr: 22%	5 yr: 30%
Sunnybrook [Klotz JCO 2015]	993	6.4 yr	10 yr: 80% 15 yr: 62%	10 yr: 98.1% 15 yr: 94.3%	–	10 yr: 36% 15 yr: 45%
UCSF [Welty J Urol 2015]	810	5.0 yr	5 yr: 98%	5 yr: 100%	5 yr: 60%	5 yr: 40%

AS = active surveillance; DRE = digital rectal examination; PSA = prostate-specific antigen.

RISK-BASED MANAGEMENT

11. In asymptomatic patients with prostate cancer and **limited life expectancy** (determined on a patient-specific basis), clinicians <u>should</u> **recommend watchful waiting**. (Strong Recommendation; Evidence Level: Grade A)

Watchful waiting does not involve routine cancer surveillance, but rather aims to deliver palliative therapy for relief of symptoms should they develop.

- maintain the patient's QOL
- avoiding treatment when prostate cancer is unlikely to cause mortality/significant morbidity avoidance of side effects from local treatment or ADT

Watchful waiting is appropriate for elderly patients or patients with significant comorbidities (of any risk level) in whom competing risks of mortality are considerably greater than the risk of death from prostate cancer.

RISK-BASED MANAGEMENT

12. For patients with **favorable intermediate-risk** prostate cancer, clinicians <u>should</u> **discuss active surveillance, radiation therapy, and radical prostatectomy**. (Strong Recommendation; Evidence Level: Grade A)

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ProtecT, Hamdy et al. N Engl J Med 2016

RISK-BASED MANAGEMENT

13. Clinicians <u>should</u> inform patients with intermediate-risk prostate cancer considering whole gland or focal ablation that there are a **lack of high-quality data comparing ablation outcomes to radiation therapy, surgery, and active surveillance**. (Expert Opinion)

The only properly powered randomized trial reported to date on prostate ablation was restricted to patients with low-risk prostate cancer and demonstrated that focal photodynamic therapy (PDT) lowered the likelihood of cancer progression and rates of surgery/radiation compared to active surveillance, at an expense of an increased likelihood of mild urinary or erectile dysfunction.

      - Not approved in the US

      - Only low-risk pts in trial, and active surveillance is preferred in low-risk

Currently, the Panel believes that ablation may be considered in select, appropriately informed patients (with clinical trial enrollment prioritized)

RISK-BASED MANAGEMENT

14. For patients with unfavorable intermediate- or high-risk prostate cancer and estimated life expectancy greater than 10 years, clinicians should offer a choice between radical prostatectomy or radiation therapy plus androgen deprivation therapy (ADT). (Strong Recommendation; Evidence Level: Grade A)

The optimal treatment for these patients remains a topic of active study, and prior published meta-analyses have reported relatively disparate findings as to comparative survival following each of these treatment approaches.

For patients with sufficiently high-risk disease, treatment with radiation and ADT can include two years of concurrent abiraterone acetate+prednisone
Clinically node-positive OR with 2 of 3 of the following:
• Clinical stage T3 or T4
• PSA $\geq$ 40ng/mL
• $\geq$ Gleason 8

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RISK-BASED MANAGEMENT

15. Clinicians should not recommend whole gland or focal ablation for patients with high-risk prostate cancer outside of a clinical trial. (Expert Opinion)
- Lack of data supporting treatment of high-risk disease with ablation

16. Clinicians may recommend palliative ADT alone for patients with high-risk prostate cancer, local symptoms, and limited life expectancy. (Expert Opinion)
- Lack of evidence indicating a significant oncologic benefit
- Thus, recommended for palliation of local disease-related symptoms in select patients

RISK LEVEL	IMAGING	OTHER TESTS	TREATMENT OPTIONS	
			Limited life expectancy	**Long life expectancy**
LOW	None	+/-Genomic testing +/- PSA density	Watchful waiting	Active surveillance preferred
FAVORABLE INTERMEDIATE	None	+/-Genomic testing	Watchful waiting	Active surveillance, Radiation therapy, or Radical prostatectomy
UNFAVORABLE INTERMEDIATE	+/- Bone scan +/- Axial imaging		Watchful waiting	Radiation therapy with ADT, or Radical prostatectomy
HIGH	Bone scan Axial imaging	+/- molecular imaging (PET) if conventional imaging is negative	Watchful waiting, or Palliative ADT if local sxs	Radiation therapy with ADT, or Radical prostatectomy

PRINCIPLES OF ACTIVE SURVEILLANCE

17. Patients managed with active surveillance should be monitored with serial PSA values and repeat prostate biopsy. (Expert Opinion)

Follow-up for active surveillance
- PSA (no more frequently than every 6 months)
- Updated symptom assessment and DRE (every 1-2 years)
- Repeat prostate biopsy

Concerns for clinical progression (serial PSA increases, DRE change) should prompt re-evaluation with MRI and possible prostate biopsy

Monitoring regimen should be individualized (by disease risk, patient risk tolerance, and life expectancy

PRINCIPLES OF ACTIVE SURVEILLANCE

18. In patients selecting active surveillance, clinicians should utilize mpMRI to augment risk stratification, but this should not replace periodic surveillance biopsy. (Expert Opinion)

MRI should be obtained if the initial (diagnostic) prostate biopsy was performed without mpMRI guidance:

- PIRADS 4 or 5
  - timely repeat (confirmatory) targeted biopsy is recommended, with disease risk re-established based on these biopsy results

- PIRADS 1, 2, or 3
  - repeat biopsy may be performed within approximately 12 months after diagnosis

Thereafter, serial surveillance biopsies are recommended every one to four years depending on patient age, health, risk of progression, and preference.

PRINCIPLES OF SURGERY

19. In patients electing radical prostatectomy, nerve-sparing, when oncologically appropriate, should be performed. (Moderate Recommendation; Evidence Level: Grade B)

- Consistently associated with decreased risk of erectile dysfunction

- Variously (but favorably) associated with improved urinary continence

- Not consistently associated with increased risk of positive surgical margins or biochemical recurrence

PRINCIPLES OF SURGERY

20. Clinicians should inform patients that pelvic lymphadenectomy provides staging information, which may guide future management, but does not have consistently documented improvement in metastasis-free, cancer-specific, or overall survival. (Moderate Recommendation; Evidence Level: Grade B)

21. Clinicians should use nomograms to select patients for lymphadenectomy. The potential benefit of identifying lymph node positive disease should be balanced with the risk of complications. (Clinical Principle)

The Benefits and Harms of Different Extents of Lymph Node Dissection During Radical Prostatectomy for Prostate Cancer: A Systematic Review

were high risks of bias and confounding in most studies. Conflicting results emerged when comparing biochemical and clinical recurrence, while no significant differences were observed among groups for survival. Conversely, the majority of studies showed that the more extensive the PLND, the greater the adverse outcomes in terms of operating time, blood loss, length of stay, and postoperative complications. No significant differences were observed in terms of urinary continence and erectile function recovery.
Conclusions: Although representing the most accurate staging procedure, PLND and its extension are associated with worse intraoperative and perioperative outcomes, whereas a direct therapeutic effect is still not evident from the current literature. The current poor quality of evidence indicates the need for robust and adequately powered clinical trials.
Patient summary: Based on a comprehensive review of the literature, this article summarizes the benefits and harms of removing lymph nodes during surgery to remove the prostate because of PCa. Although the quality of the data from the studies was poor, the review suggests that lymph node removal may not have any direct benefit on cancer outcomes and may instead result in more complications. Nevertheless, the procedure

Updated Nomogram Predicting Lymph Node Invasion in Patients with Prostate Cancer Undergoing Extended Pelvic Lymph Node Dissection: The Essential Importance of Percentage of Positive Cores

Alberto Briganti [a,*], Alessandro Larcher [a], Firas Abdollah [a], Umberto Capitanio [a], Andrea Gallina [a], Nazareno Suardi [a], Marco Bianchi [a], Maxine Sun [c], Massimo Freschi [b], Andrea Salonia [a], Pierre I. Karakiewicz [c], Patrizio Rigatti [a], Francesco Montorsi [a]
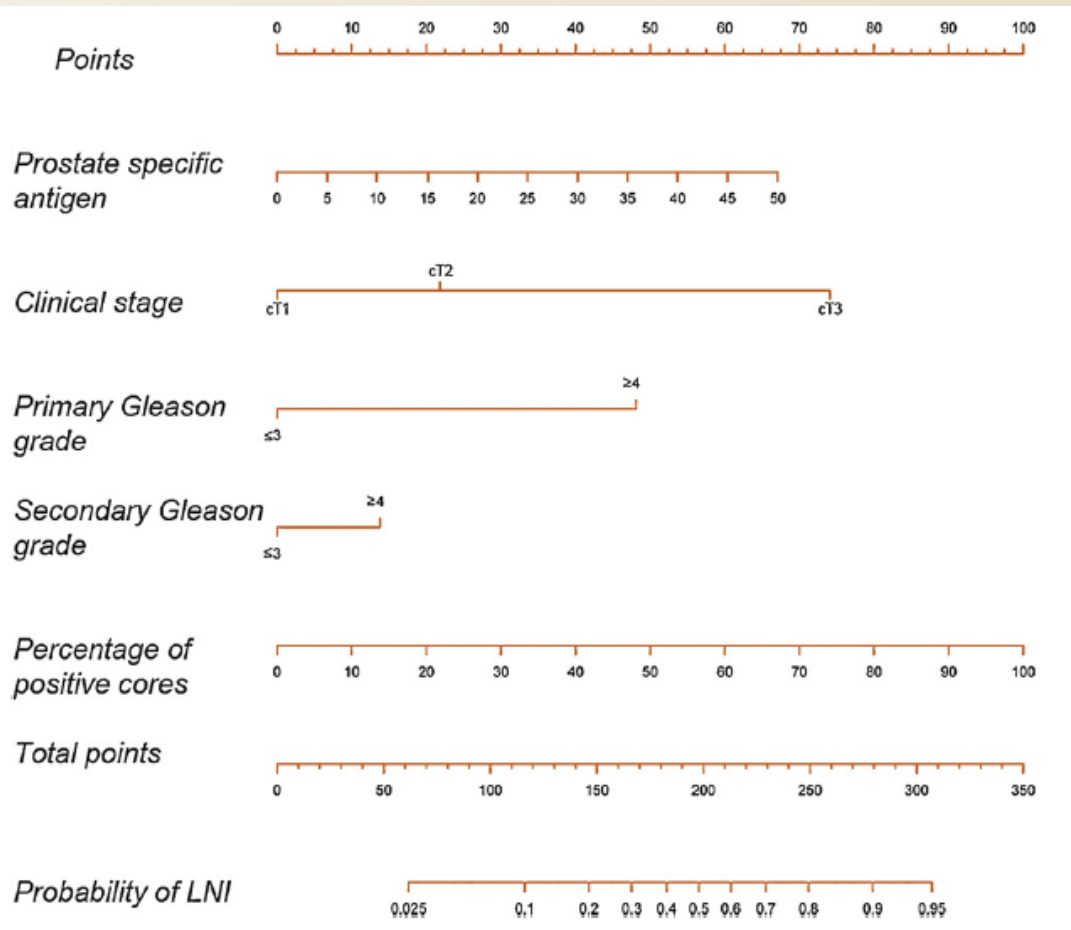
Model developed in 588 patients undergoing ePLND

Predictive accuracy = 87.6%

Suggests using 5% threshold from model for ePLND
-Spare 65.5% from LND
-Miss only 1.5% of (+) LN

Eur Urol 2012

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Kenneth J. Pienta,* Michael A. Gorin,† Steven P. Rowe, Peter R. Carroll,‡ Frédéric Pouliot,§ Stephan Probst, Lawrence Saperstein, Mark A. Preston, Ajjai S. Alva,‖ Akash Patnaik, Jeremy C. Durack,¶ Nancy Stambler,** Tess Lin,** Jessica Jensen,** Vivien Wong,** Barry A. Siegel,**,†† Michael J. Morris,**,‡‡ and OSPREY Study Group

J Urol 2021

Diagnostic Accuracy of ^{68}Ga-PSMA-11 PET for Pelvic Nodal Metastasis Detection Prior to Radical Prostatectomy and Pelvic Lymph Node Dissection
A Multicenter Prospective Phase 3 Imaging Trial

Hope TA et al, JAMA Oncol 2021

- 252 patients with high-risk prostate cancer underwent scan + RP/PLND

- Detection of positive lymph nodes:
  - **Sensitivity = 40.3%**

> ease is present. On the other hand, the NPV was 0.81, indicating that 20% of patients who underwent prostatectomy with a negative PET will have nodes on pathology. For this reason, it is important that surgeons do not use a negative PET to forgo a pelvic nodal dissection. Prospective trials based on PSMA PET

- 277 men with intermediate (18%) or high risk (81%) disease

- Detection of positive lymph nodes:
  - **Sensitivity = 40%**
  - Specificity = 95%
  - PPV = 75%
  - **NPV = 81%**

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WHEN TO DO A LND AT PROSTATECTOMY

- Existing guidelines have suggested nomogram-predicted thresholds of LN (+) disease from 2-7%

- Panel recommends shared-decision making with patient, including discussion of:
  - Risk of harboring LN (+) disease
  - Utility of identifying LN (+) disease
 - Risks of LND: increased surgical time, lymphocele

PRINCIPLES OF SURGERY

22. Clinicians performing pelvic lymphadenectomy <u>should</u> **perform an extended dissection**, which improves staging accuracy compared to a limited dissection. (Moderate Recommendation; Evidence Level: Grade: B)

- Removing more nodes increases likelihood of detecting positive nodes
- But no randomized study has shown an oncologic benefit to extended vs. standard

Toujier et al Euro Urol Oncol 2021
Lestigni et al Euro Urol 2021

FIG. 2. Predicted probability of finding positive LN by number of nodes removed.
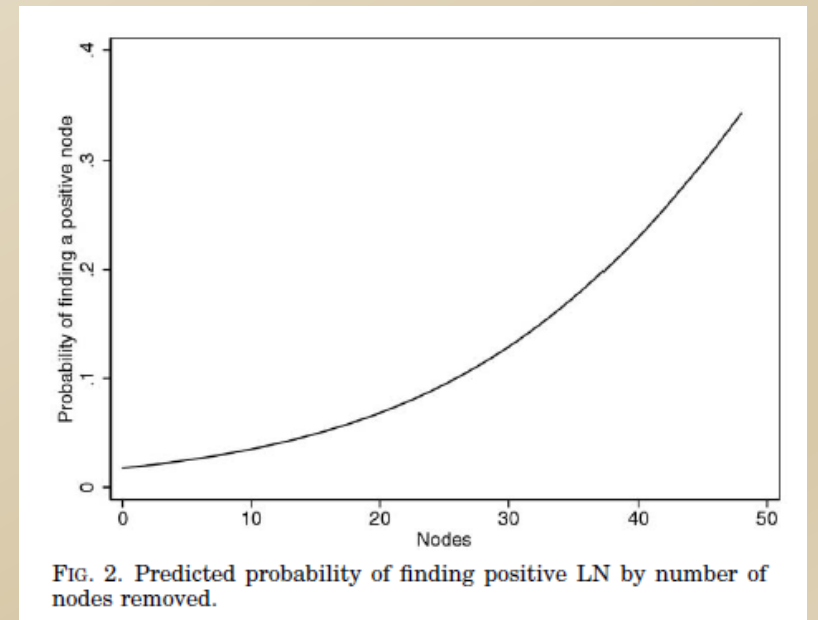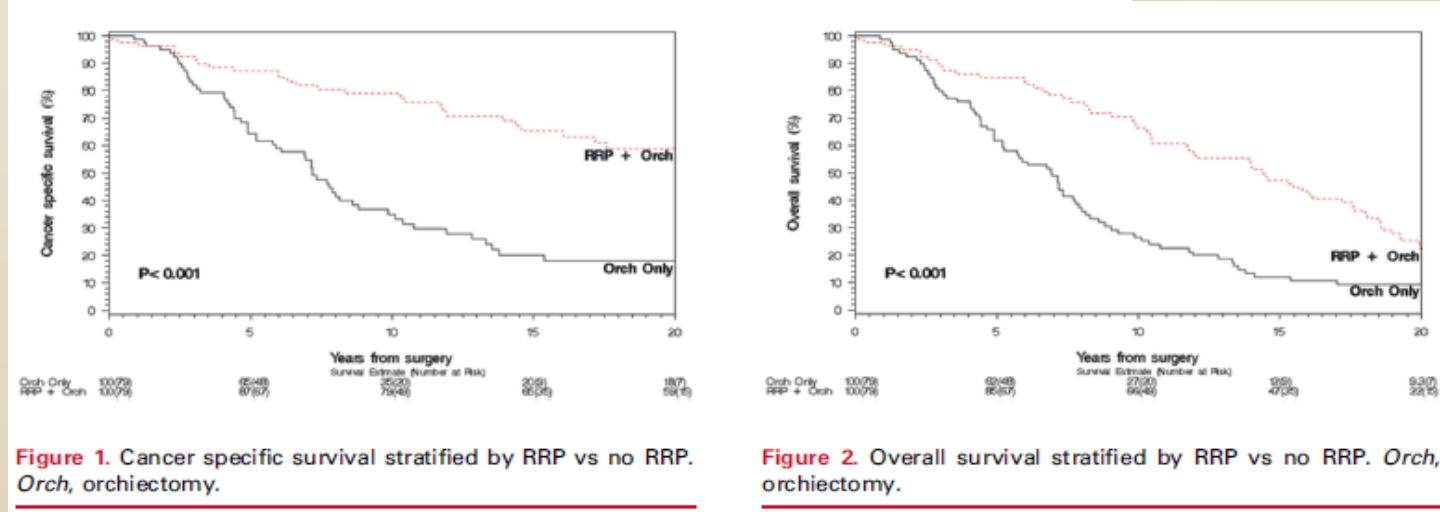
Masterson TA et al, J Urol 2006

PRINCIPLES OF SURGERY

23. Clinicians <u>should</u> **complete a radical prostatectomy if suspicious regional nodes are encountered intraoperatively**. (Moderate Recommendation; Evidence Level: Grade C)

Impact of Radical Prostatectomy on Long-Term Oncologic Outcomes in a Matched Cohort of Men with Pathological Node Positive Prostate Cancer Managed by Castration

Bimal Bhindi, Laureano J. Rangel, Ross J. Mason, Matthew T. Gettman, Igor Frank, Eugene D. Kwon, Matthew K. Tollefson, R. Houston Thompson, Stephen A. Boorjian* and R. Jeffrey Karnes†

J Urol 2017

Figure 1. Cancer specific survival stratified by RRP vs no RRP. *Orch*, orchiectomy.

Figure 2. Overall survival stratified by RRP vs no RRP. *Orch*, orchiectomy.

PRINCIPLES OF SURGERY

24. Clinicians <u>should</u> **risk stratify patients with positive lymph nodes** identified at radical prostatectomy based on pathologic variables and postoperative PSA. (Expert Opinion)

25. Clinicians <u>may offer</u> patients with positive lymph nodes identified at radical prostatectomy and an undetectable post-operative PSA **adjuvant therapy or observation**. (Conditional Recommendation; Evidence Level: Grade C)

Immediate versus deferred androgen deprivation treatment in patients with node-positive prostate cancer after radical prostatectomy and pelvic lymphadenectomy

- Edward M Messing, Judith Manola, Jorge Yao, Maureen Kiernan, David Crawford, George Wilding, P Anthony di'SantAgnese, Donald Trump, on behalf of the Eastern Cooperative Oncology Group study EST 3886

Small sample size

No comparison of adjuvant ADT to ADT at BCR (early salvage)
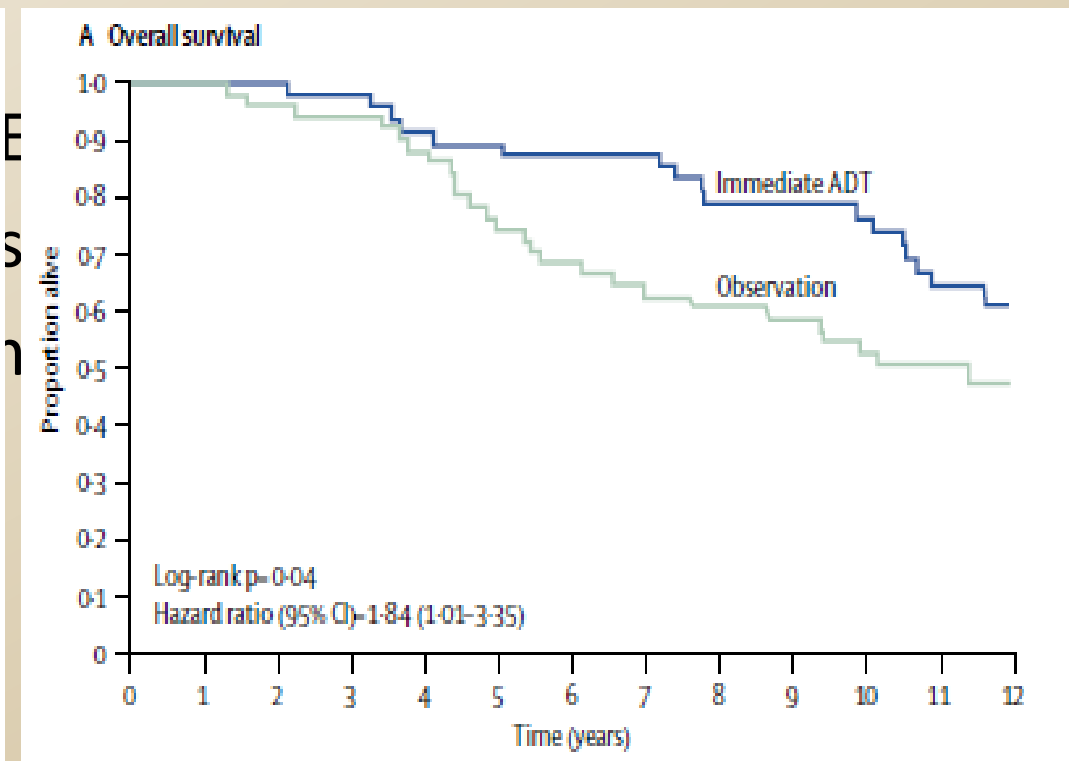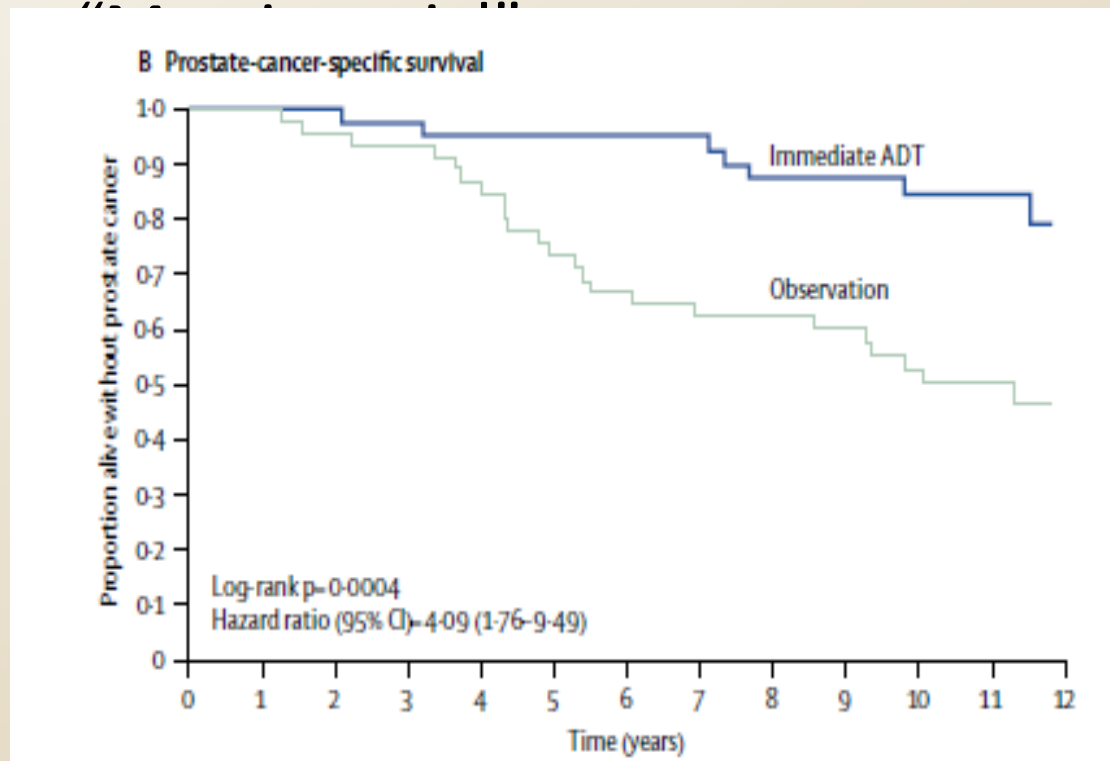
SURVIVAL AFTER RP WITH LN+: DO WE ALWAYS NEED MORE THAN SURGERY? (THERAPEUTIC BENEFIT TO LND?)

- **Palapattu et al (JHH)**
  - 26.5% BCR-free at 5 yrs without adj rx
  - 43% BCR-free at 5 yrs if LND < 15%

- **Touijer et al (MSKCC)**
  - 28% 10-year BCR-free survival and 72% CSS without adjuvant tx
  - 59% had only 1 (+) LN

- **Seiler et al (Bern)**
  - If single node (+), 57% free of ADT, and CSM 31% at 15.6 yrs f/u

Impact of Adjuvant Radiotherapy on Survival of Patients With Node-Positive Prostate Cancer

Firas Abdollah, R. Jeffrey Karnes, Nazareno Suardi, Cesare Cozzarini, Giorgio Gandaglia, Nicola Fossati, Damiano Vizziello, Maxine Sun, Pierre I. Karakiewicz, Mani Menon, Francesco Montorsi, and Alberto Briganti

- Who specifically with N+ disease benefits from aRT?
  - ≤ 2 positive LN; GS 7-10; pT3b/pT4 or PSM
  - 3-4 positive LN
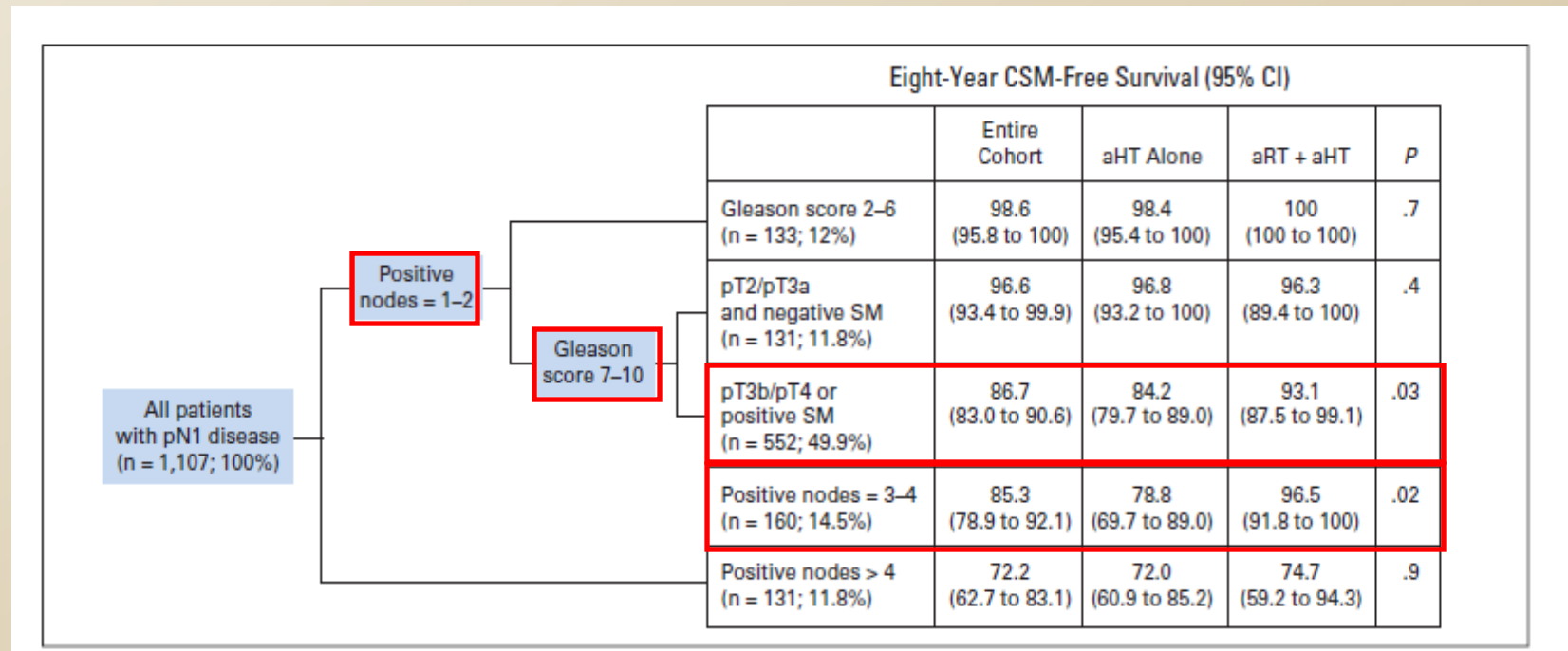
WHAT TO DO WITH (+) LN AFTER SURGERY?

- Individualized approach

- Undetectable initial PSA with limited nodal burden + absence of high-risk features in primary tumor → consider surveillance

- Adjuvant therapies (ADT, RT) with increased # positive nodes, high risk primary tumor features

- Balanced discussion of treatment benefits vs toxicities

PRINCIPLES OF SURGERY

26. Clinicians should not routinely recommend adjuvant radiation therapy after radical prostatectomy. (Strong Recommendation; Evidence Level: Grade A)

- 2153 patients from 3 RCTs

- No evidence that event-free survival improved with adjuvant versus early salvage RT

Adjuvant or early salvage radiotherapy for the treatment of localised and locally advanced prostate cancer: a prospectively planned systematic review and meta-analysis of aggregate data

Claire L Vale, David Fisher, Andrew Kneebone, Christopher Parker, Maria Pearse, Pierre Richaud, Paul Sargos, Matthew R Sydes, Christopher Brawley, Meryem Brihoum, Chris Brown, Sylvie Chabaud, Adrian Cook, Silvia Forcat, Carol Fraser-Browne, Igor Latorzeff, Mahesh K B Parmar, Jayne F Tierney, for the ARTISTIC Meta-analysis Group

	Events/patients		HR (95% CI)	Weight
	Early salvage radiotherapy	Adjuvant radiotherapy		
RADICALS-RT	82/699	87/697	1·10 (0·81–1·49)	64·28%
GETUG-AFU 17	26/212	14/212	0·57 (0·30–1·08)	14·55%
RAVES	30/167	25/166	0·87 (0·51–1·48)	21·17%
			0·95 (0·75–1·21)	100·00%

Favours adjuvant radiotherapy   Favours early salvage radiotherapy
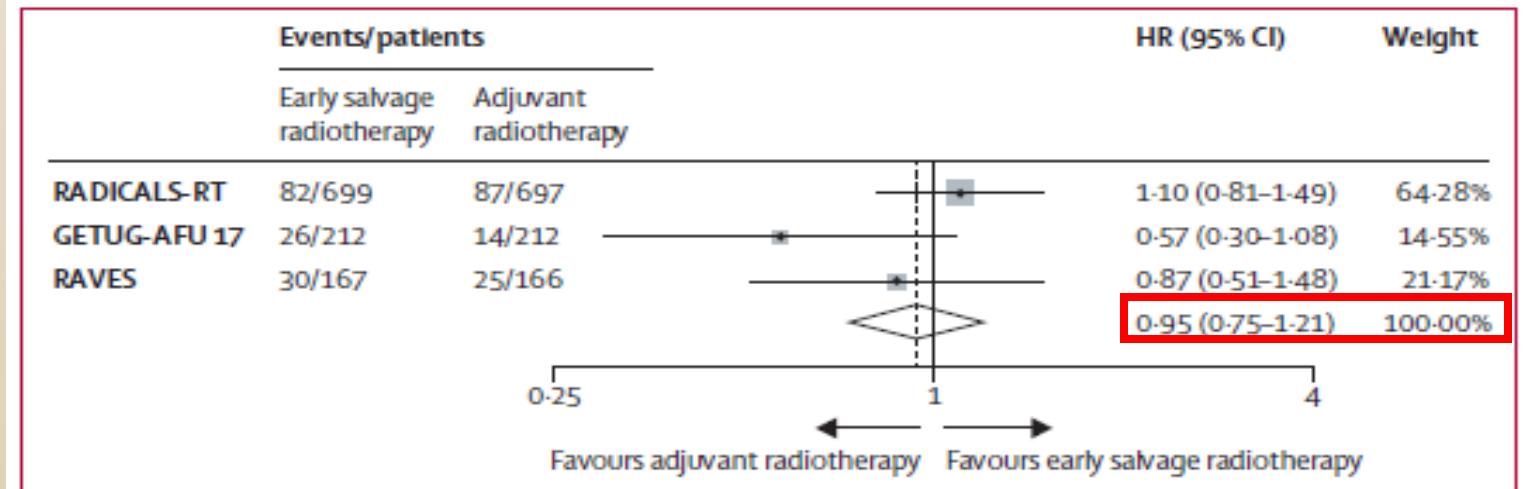
Figure 2: Effect of radiotherapy timing on event-free survival

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PRINCIPLES OF SURGERY: CONCLUSIONS

- Nerve-sparing should be performed when oncologically feasible, as associated with improved postoperative quality of life outcomes

- Lymph nodes:
  - Use nomograms to calculate risk of harboring (+) nodes

  - Discuss benefits of finding (+) nodes [staging, inform secondary therapy], absence of documented survival benefit, complication risk

  - When lymph node dissection performed → should be extended

  - Complete surgery even if suspicious nodes encountered intraoperatively

PRINCIPLES OF SURGERY: CONCLUSIONS

- Postoperatively:
  - Risk stratify management of patients with positive lymph nodes at surgery
  - Pathology (# positive nodes, primary tumor features) + post-op PSA

- Patients with (+) LN and an undetectable post-op PSA:
  - Offer adjuvant therapy or surveillance

- Adjuvant RT should not be routinely used after prostatectomy

PRINCIPLES OF RADIATION: BEST PRACTICES

27.Clinicians should utilize available target localization, normal tissue avoidance, simulation, advanced treatment planning/delivery, and image-guidance procedures to optimize the therapeutic ratio of external beam radiation therapy (EBRT) delivered for prostate cancer. (Clinical Principle)

- **Simulation procedures:** bladder/rectum filling instructions, patient immobilization, placement of fiducial markers, and use of rectal spacers

- **Imaging procedures:** Computed tomography (CT) simulations, integrations of fusion imaging (e.g., magnetic resonance imaging [MRI prostate), image-guided radiation therapy approaches (e.g., cone-beam CT)

- **Planning procedures:** Use of highly conformal radiation therapy such as intensity-modulated radiation therapy (IMRT), volumetric modulated arc therapy (VMAT), and stereotactic body radiation therapy (SBRT), combined with published target and normal tissue dose objectives to optimize planning

PRINCIPLES OF RADIATION: DOSE ESCALATION

28. Clinicians <u>should</u> **utilize dose escalation when EBRT is the primary treatment** for patients with prostate cancer. (Strong Recommendation; Evidence Level: Grade A)

JAMA Oncology | Original Investigation

Effect of Standard vs Dose-Escalated Radiation Therapy for Patients With Intermediate-Risk Prostate Cancer
The NRG Oncology RTOG 0126 Randomized Clinical Trial

Jeff M. Michalski, MD, MBA; Jennifer Moughan, MS; James Purdy, PhD; Walter Bosch, DSc;
Deborah W. Bruner, PhD; Jean-Paul Bahary, MD; Harold Lau, MD; Marie Duclos, MD; Matthew Parliament, MD;
Gerard Morton, MD; Daniel Hamstra, MD; Michael Seider, MD; Michael I. Lock, MD; Malti Patel, MD;
Hiram Gay, MD; Eric Vigneault, MD; Kathryn Winter, MS; Howard Sandler, MD

- Dose escalation improved rates of biochemical failure and distant metastases (though no difference in OS)
- No impact of dose escalation on relevant PROs

JAMA Oncol 2018

B Phoenix criteria

	Failed	Total
70.2 Gy	268	751
79.2 Gy	156	748

HR = 0.54 (95% CI, 0.44-0.65)
Gray test P <.001
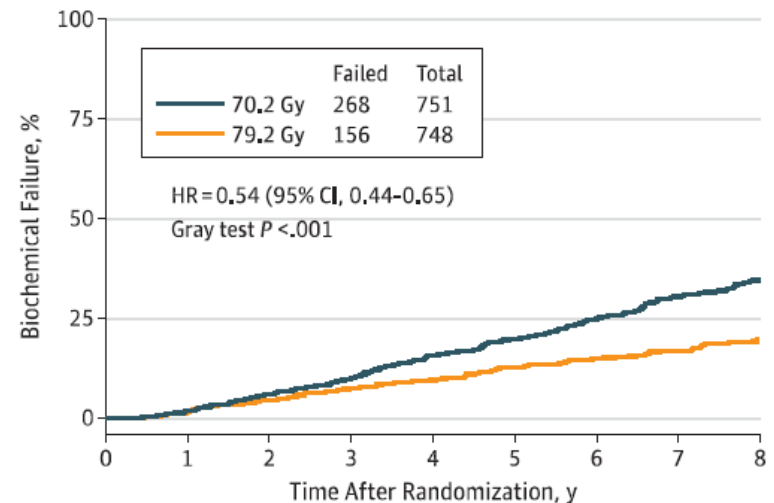
No. at risk

70.2 Gy	751	722	666	619	553	495	433	358	259
79.2 Gy	748	719	677	632	588	536	492	430	317

PRINCIPLES OF RADIATION: PROTON NO BETTER

29. Clinicians <u>may counsel patients</u> with prostate cancer that **proton therapy is a treatment option, but it has not been shown to be superior to other radiation modalities in terms of toxicity profile and cancer outcomes.** (Conditional Recommendation; Evidence Level: Grade C)

No difference in overall urinary, bowel, sexual on EPIC

TABLE 3. Percentage of Men With Minimally Detectable Differences From Their Baseline Expanded Prostate Cancer Index Composite Scores[a]

EPIC Domain at Follow-Up Periods	PT, %	IMRT, %	P[b]
Bowel summary			
6 mo	25	39	.002
1 y	41	37	.99
2 y	37	38	.99
Urinary incontinence			
6 mo	22	28	.36
1 y	31	29	.99
2 y	32	34	.99
Urinary irritative/obstructive			
6 mo	18	25	.99
1 y	23	20	.99
2 y	17	18	.99
Sexual summary			
6 mo	27	31	.99
1 y	36	36	.99
2 y	40	41	.99

Abbreviations: EPIC, Expanded Prostate Cancer Index Composite; IMRT, intensity-modulated radiotherapy; PT, Proton Therapy.
[a] These represent declines in scores >50% from baseline.
[b] P values were determined using the Wilcoxon rank-sum test with Bonferonni adjustment.

Hoppe et al. Cancer 2014

PRINCIPLES OF RADIATION: MODERATE HYPOFRACTIONATION

30. Clinicians <u>should offer</u> **moderate hypofractionated EBRT for patients with low- or intermediate-risk prostate cancer who elect EBRT**. (Strong Recommendation; Evidence Level: Grade A)

Hickey et al. Cochrane Systematic Review 2019 Hypofractionated (>2Gy/fraction, range 2.35-3.4Gy) v. Conventional Fractionated (1.8-2Gy) 10 Randomized Trials, N=8,278	
Biochemical recurrence-free survival	HR 1.14, 95% CI 0.88 to 1.47, 5 trials
Metastasis-free survival	HR 0.93, 95% CI 0.57 to 1.45, 5 trials
Prostate cancer-specific survival	HR 1.00, 95% CI 0.72 to 1.39, 8 trials
Overall survival	HR 1.06, 95% CI 0.93 to 1.20, 10 trials

No differences in acute GU, late GU, late GI toxicities

PRINCIPLES OF RADIATION: ULTRA-HYPOFRACTIONATION

31. Clinicians <u>may offer</u> **ultra hypofractionated EBRT for patients with low- or intermediate risk prostate cancer who elect EBRT**. (Conditional Recommendation; Evidence Level: Grade B)

HYPO-RT n=1,200	
Ultra hypofractionation (42.7Gy in 7 fractions [6.1 Gy]) Conventional fractionation (78.0 Gy in 39 fractions [2 Gy])	
Failure-free survival	HR 1.00, 95% CI 0.76 to 1.32
Prostate cancer mortality	Incidence at 5 years 2% v. 1% p=0.46
Overall survival	HR 1.11, 95% CI 0.73 to 1.69
Ultra found to be non-inferior but was associated with **increased incidence acute bowel symptoms** on PROs but no diff in late urinary, bowel, sexual problems.	

Widmark et al. Lancet 2019
Fransson et al. Lancet Oncol 2021

PRINCIPLES OF RADIATION

32. In patients with <u>low- or favorable intermediate-risk</u> prostate cancer electing radiation therapy, clinicians should **offer dose-escalated hypofractionated EBRT (moderate or ultra), permanent low-dose rate (LDR) seed implant, or temporary high-dose rate (HDR) prostate implant as equivalent forms of treatment**. (Strong Recommendation; Evidence Level: Grade B)

32. In patients with <u>low- or intermediate-risk</u> prostate cancer electing radiation therapy, clinicians **should not electively radiate pelvic lymph nodes**. (Strong Recommendation; Evidence Level: Grade B)

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GETUG-01: Pommier et al. Int J Radiat Oncol 2016
RTOG 9413 Roach et al. Lancet Oncol 2018

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PRINCIPLES OF RADIATION: USE OF ADT

34. In patients with <u>low- or favorable intermediate-risk</u> prostate cancer electing radiation therapy, clinicians **should not routinely use ADT**. (Moderate Recommendation; Evidence Level: Grade B)

ADT is associated with well-recognized side effects that may impact QOL

- **Decreased libido**
- **Hot flashes**
- **Depression/mood disturbances**
- **Fatigue**
- **Weight gain**
- **Loss of muscle, bone mass**
- **Cognitive side effects**
- **Cardiovascular events**

- Excellent outcomes with RT monotherapy.

- Awaiting favorable intermediate risk sub-group analysis from RTOG 0815.

PRINCIPLES OF RADIATION: USE OF ADT

35. In patients with <u>unfavorable intermediate-risk</u> prostate cancer electing radiation therapy, **clinicians should offer the addition of short-course (four to six months) ADT with radiation therapy**. (Strong Recommendation; Evidence Level: Grade A)
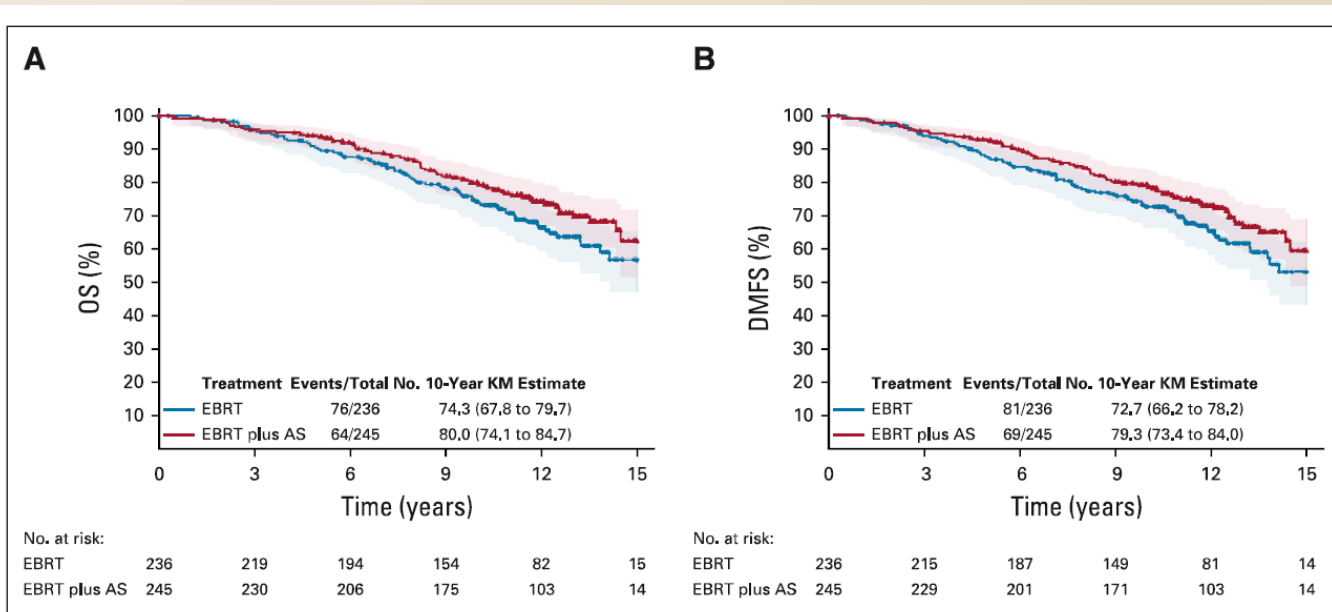
481 intermediate-risk patients
Median 12.2 yrs follow-up
Randomized to 6 mo ADT or none

EORTC 22991 showed:
- 10yrEFS 68.1% vs 49.3%
- 10yrDFS 79.3% vs 72.7%
- 10yrOS 80.0% vs 74.3%

Bolla et al. JCO 2021

FIG 3. (A) OS by treatment arm in the intent-to-treat population. HR (EBRT plus AS v EBRT) = 0.74 (95% CI, 0.53 to 1.04); P = .082. (B) DMFS by treatment arm in the intent-to-treat population. HR (EBRT plus AS v EBRT) = 0.74 (95% CI, 0.53 to 1.02); P = .065. AS, androgen suppression; DMFS, distant metastasis–free survival; EBRT, external-beam radiotherapy; HR, hazard ratio; KM, Kaplan Meier; OS, overall survival.

DEPARTMENT OF UROLOGY

PRINCIPLES OF RADIATION

36. Clinicians <u>should offer</u> **moderate hypofractionated EBRT for patients with high-risk prostate cancer who are candidates for EBRT**. (Moderate Recommendation; Evidence Level: Grade C)

Outcome	No. of Events C-IMRT H-IMRT	HR H-IMRT v C-IMRT	Ethnicity-Adjusted HR (95% CI)
BCDF	31 36		1.32 (0.81 to 2.16)
BF	25 28		1.23 (0.71 to 2.13)
Local recurrence	7 6		0.89 (0.28 to 2.83)
Metastases	11 21		1.96 (0.93 to 4.14)
PCSM	8 7		0.95 (0.34 to 2.67)
Overall mortality	40 51		1.41 (0.93 to 2.16)

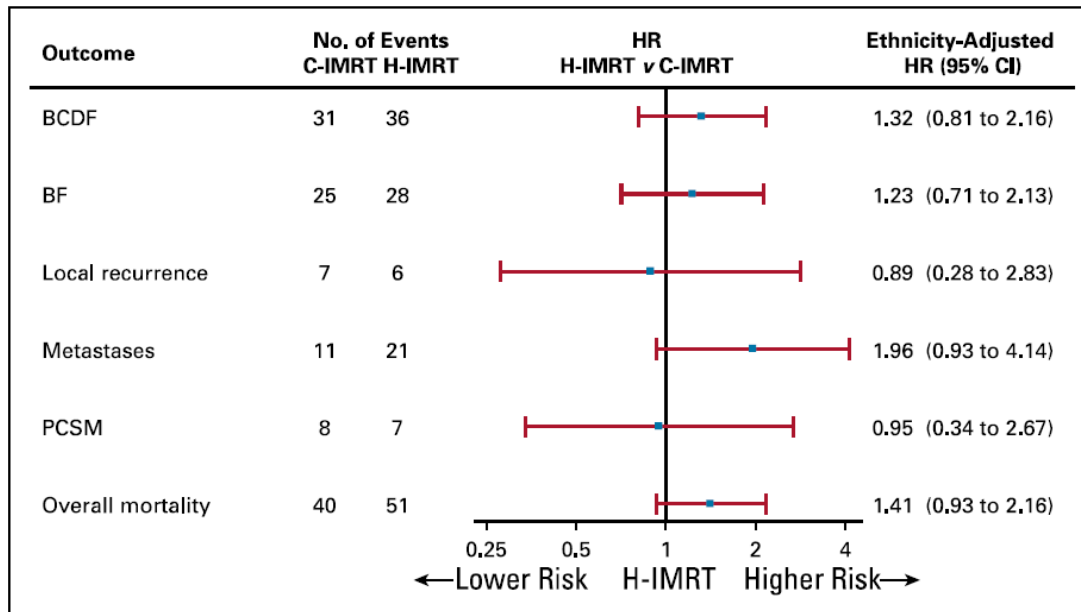0.25 0.5 1 2 4
←Lower Risk H-IMRT Higher Risk→

FIG 3. Forest plot of outcomes. BCDF, biochemical and/or clinical failure; BF, biochemical failure; C-IMRT, conventionally fractionated intensity-modulated radiation therapy; H-IMRT, moderate hypofractionated intensity-modulated radiation therapy; HR, hazard ratio; PCSM, prostate cancer–specific mortality.

Single institution
Only 86 men with high-risk

Avkshtol et al. J Clin Oncol 2020

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PRINCIPLES OF RADIATION

37. In patients with <u>unfavorable intermediate- or high-risk</u> prostate cancer electing radiation therapy, clinicians **should offer dose-escalated hypofractionated EBRT or combined EBRT + brachytherapy (LDR, HDR) along with a risk-appropriate course of ADT**. (Strong Recommendation; Evidence Level: Grade A/B)

38. In patients with <u>high-risk</u> prostate cancer electing radiation therapy, clinicians **may offer radiation to the pelvic lymph nodes**. (Conditional Recommendation; Evidence Level: Grade B)

PRINCIPLES OF RADIATION: ADT IN HIGH-RISK

40. In patients with <u>high-risk</u> prostate cancer electing radiation therapy, clinicians **should recommend the addition of long-course (18 to 36 months) ADT with radiation therapy**. (Strong Recommendation; Evidence Level: Grade A)

EORTC 22863 n=415, locally advanced prostate cancer	
70Gy prostate radiation therapy plus 3 years of ADT Radiation therapy alone	
Prostate cancer-specific survival	HR 0.38, 95% CI 0.24 to 0.60
Overall survival	HR 0.60, 95% CI 0.45 to 0.80
This study established 3 years of ADT as a reference standard for the duration of combined ADT with radiation therapy in the treatment of patients with high-risk disease.	

Ataman et al. Eur J Cancer 2004
Bolla et al. Lancet 2002
Bolla et al. Lancet Oncol 2010
Bolla et al. J Clin Oncol 2016

FOLLOW-UP AFTER TREATMENT

43. Clinicians <u>should</u> **monitor patients with prostate cancer post therapy with PSA and symptom assessment**. (Clinical Principle)

- The specific intervals may be tailored to disease risk based on clinicopathologic feature, age, comorbidity status, preference.

PSA Follow-up Schedule	
Years 1-2	Every 3-6 months
Years 2-5	Every 6 months
Years 5-10	Annually
Years 10+	Shared decision-making*

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FOLLOW-UP AFTER TREATMENT

44. Clinicians should support patients with prostate cancer through continued **symptom management and encouraging engagement with professional or community-based resources**. (Clinical Principle)

Resources may be engaged at any point (early diagnosis, treatment, post-treatment)

- Social work services
- Cancer support groups
- Patient advocacy organizations
- Physical/lifestyle survivorship
  - Dietary/nutritional services
  - Physical therapy
  - Pelvic floor rehabilitation
  - Psychosexual therapy

FUTURE DIRECTIONS

- Treatment Intensification for High-Risk Disease

- Genomic Classifiers

- Advanced Imaging

TREATMENT INTENSIFICATION FOR HIGH-RISK DISEASE
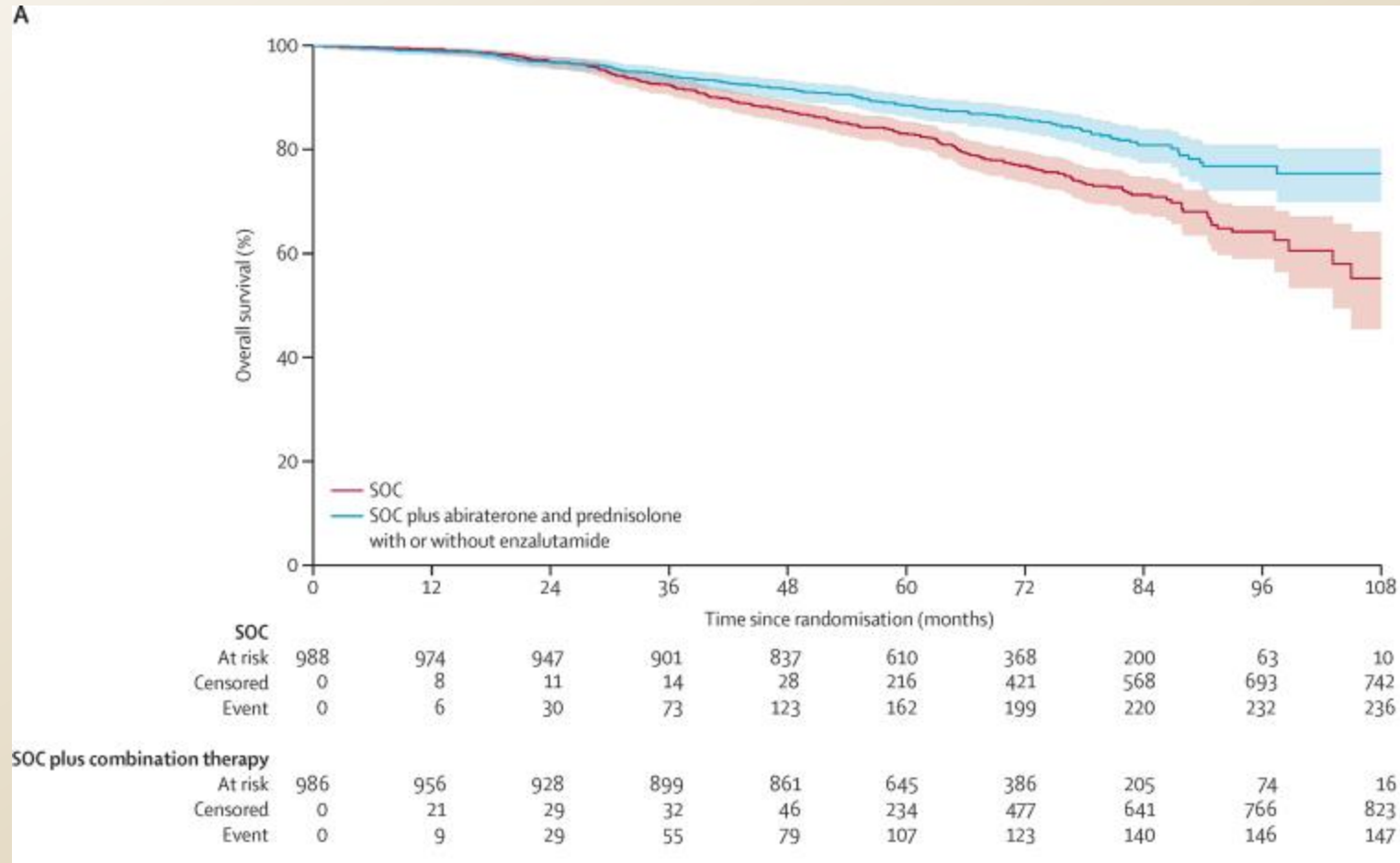
The STAMPEDE trial results showing an overall survival benefit to the **addition of 2 years of abiraterone acetate plus prednisolone to ADT to definitive prostate radiation in very high-risk localized and node positive disease** has ignited interest in treatment intensification in this patient population.

Attard et al. Lancet 2022

TREATMENT INTENSIFICATION FOR HIGH-RISK DISEASE

- **ENZARAD:** Enzalutamide in ADT with radiation therapy for high-risk localized prostate cancer

- **PROTEUS:** Apalutamide + ADT versus placebo + ADT prior to radical prostatectomy in localized high-risk or locally advanced disease *(peri-operative treatment)*

- **DASL-HiCaP:** darolutamide in very high-risk localized and biochemically recurrent/persistent disease *(salvage and high risk localized disease)*

- **NRG-GU009:** Parallel Phase III Randomized Trials for High Risk Prostate Cancer Evaluating De-Intensification for Lower Genomic Risk and Intensification of Concurrent Therapy for Higher Genomic Risk with Radiation (PREDICT-RT*) **(high risk localized disease)**

GENOMIC CLASSIFIERS

Limitation of the existing data supporting the prognostic capacity of GCs is that **studies have been primarily based on tissue analysis of radical prostatectomy specimens** rather than biopsy specimens.

NRG GU009 and 010
- Evaluating treatment intensification and de-intensification in intermediate and high-risk patients undergoing radiation
  - I.e., whether to use ADT and for how long
- Based on prostate RNA expression (Decipher^{TM}) in biopsy specimens

ADVANCED IMAGING

ADVANCED IMAGING

Novel imaging radiotracers utilizing PET-based technology have emerged and are FDA approved for clinical use. PSMA-based PET imaging tracers include:

- **Gallium 68 PSMA-11 (Ga 68 PSMA-11)**
- **Piflufolastat F-18 (18F-DCFPyL)**

In the OSPREY study, of the 268 men with high-risk PCa imaged with 18F-DCFPyL-PET/CT, 252 had evaluable histopathology for determining the diagnostic performance of 18F-DCFPyL-PET in identifying pelvic nodal metastases.
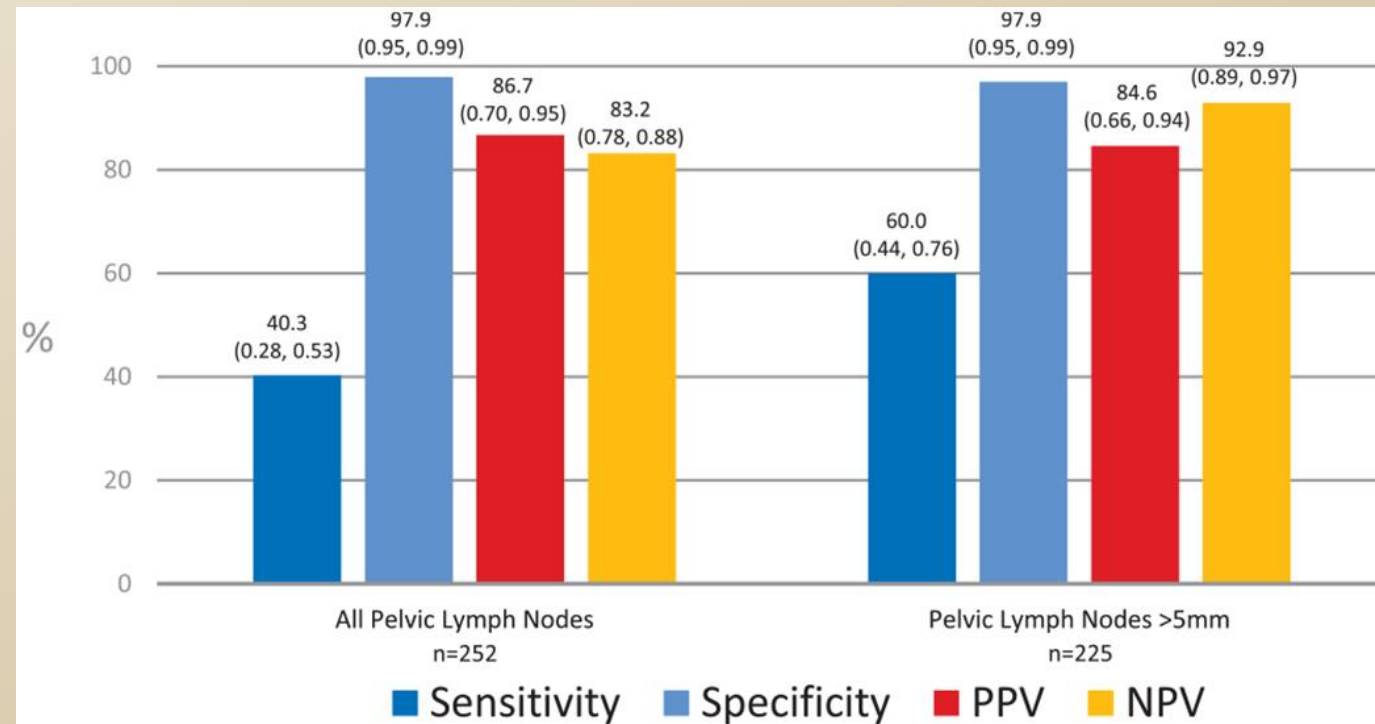
Thank You

Clinically Localized Prostate Cancer Panel

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Stephen Boorjian, MD (Vice Chair)

Philip M. Pierorazio, MD (PGC Rep)

Tony Crispino (Patient Advocate)

Gregory Auffenberg, MD

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