EARLY STAGE PROSTATE CANCER: MANAGEMENT DECISIONS - EFFICACY VS QUALITY OF LIFE CONSIDERATIONS

Presenters & Disclosures

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- Nothing to disclose.

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- Nothing to disclose.

Outline

- Risk Stratification
- Technics:
  - Active surveillance
  - Cryotherapy
  - High Intensity Focused Ultrasound (HI-FU)
  - Surgery
  - External Beam Radiotherapy (EBRT)
  - Brachytherapy (“Seeds”)
  - Combination Radiation
- Comparative Outcomes
  - Surgery Vs Radiation
  - Different Types of Radiation

Risk Groups - American Urologic Association

TABLE 3: Risk Stratification for Localized Prostate Cancer	
Very Low Risk	PSA <10 ng/ml AND Grade Group 1 AND clinical stage T1-T2a AND <34% of biopsy cores positive AND no core with >50% involved, AND PSA density <0.15 ng/ml/cc
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) OR Grade Group 2 (with PSA<10) - Unfavorable: Grade Group 2 (with either PSA 10-<20 or clinical stage T2b-c) OR Grade Group 3 (with PSA < 20)
High Risk	PSA ≥20 ng/ml OR Grade Group 4-5 OR clinical stage ≥T3*
*Clinical stage T3 cancer is considered locally advanced and, therefore, outside the scope of this guideline.	

Risk Groups - NCCN

Risk Group	Clinical/Pathologic Features See Staging (ST-1)			Additional Evaluation[g,h]
Very low[e]	Has all of the following: • cT1c • Grade Group 1 • PSA <10 ng/mL • Fewer than 3 prostate biopsy fragments/cores positive, ≤50% cancer in each fragment/core[f] • PSA density <0.15 ng/mL/g			• Consider confirmatory prostate biopsy ± mpMRI if not performed prior to biopsy to establish candidacy for active surveillance
Low[e]	Has all of the following but does not qualify for very low risk: • cT1–cT2a • Grade Group 1 • PSA <10 ng/mL			• Consider confirmatory prostate biopsy ± mpMRI if not performed prior to biopsy to establish candidacy for active surveillance
Intermediate[e]	Has all of the following: • No high-risk group features • No very-high-risk group features • Has one or more intermediate risk factors (IRFs): ▸ cT2b–cT2c ▸ Grade Group 2 or 3 ▸ PSA 10–20 ng/mL	Favorable intermediate	Has all of the following: • 1 IRF • Grade Group 1 or 2 • <50% biopsy cores positive (eg, <6 of 12 cores)[f]	• Consider confirmatory prostate biopsy ± mpMRI if not performed prior to biopsy for those considering active surveillance
		Unfavorable intermediate	Has one or more of the following: • 2 or 3 IRFs • Grade Group 3 • ≥ 50% biopsy cores positive (eg, ≥ 6 of 12 cores)[f]	Bone and soft tissue imaging[i,j] • If regional or distant metastases are found, see PROS-8 or PROS-12
High	Has no very-high-risk features and has exactly one high-risk feature: • cT3a OR • Grade Group 4 or Grade Group 5 OR • PSA >20 ng/mL			Bone and soft tissue imaging[i,j] • If regional or distant metastases are found, see PROS-8 or PROS-12
Very high	Has at least one of the following: • cT3b–cT4 • Primary Gleason pattern 5 • 2 or 3 high-risk features • >4 cores with Grade Group 4 or 5			Bone and soft tissue imaging[i,j] • If regional or distant metastases are found, see PROS-8 or PROS-12

Summary of Treatment Selection

- Active Surveillance preferred for low risk and can be considered in select favorable intermediate risk

		Risk Group			
		Low	Fav Int	Unfav Int	High
Treatment	Prostatectomy	x	x	x	x
	EBRT Alone	x	x		
	Brachy Alone	x	x		
	SBRT Alone	x	x		
	SBRT + ADT			x	
	XRT+ADT			x	x
	XRT+Brachy+ADT			x	x

Determining Life Expectancy

- Start with the SS Life Index Life Expectancy
  - Add 50% if they are in the top quartile of health
  - Subtract 50% if they are in the bottom quartile of health

- At what age does an average health man have a 20 year life expectancy?
- 62
- At what age does an average health man have a 10 year life expectancy?
- 77
- At what age does an average health man have a 5 year life expectancy?
- 87

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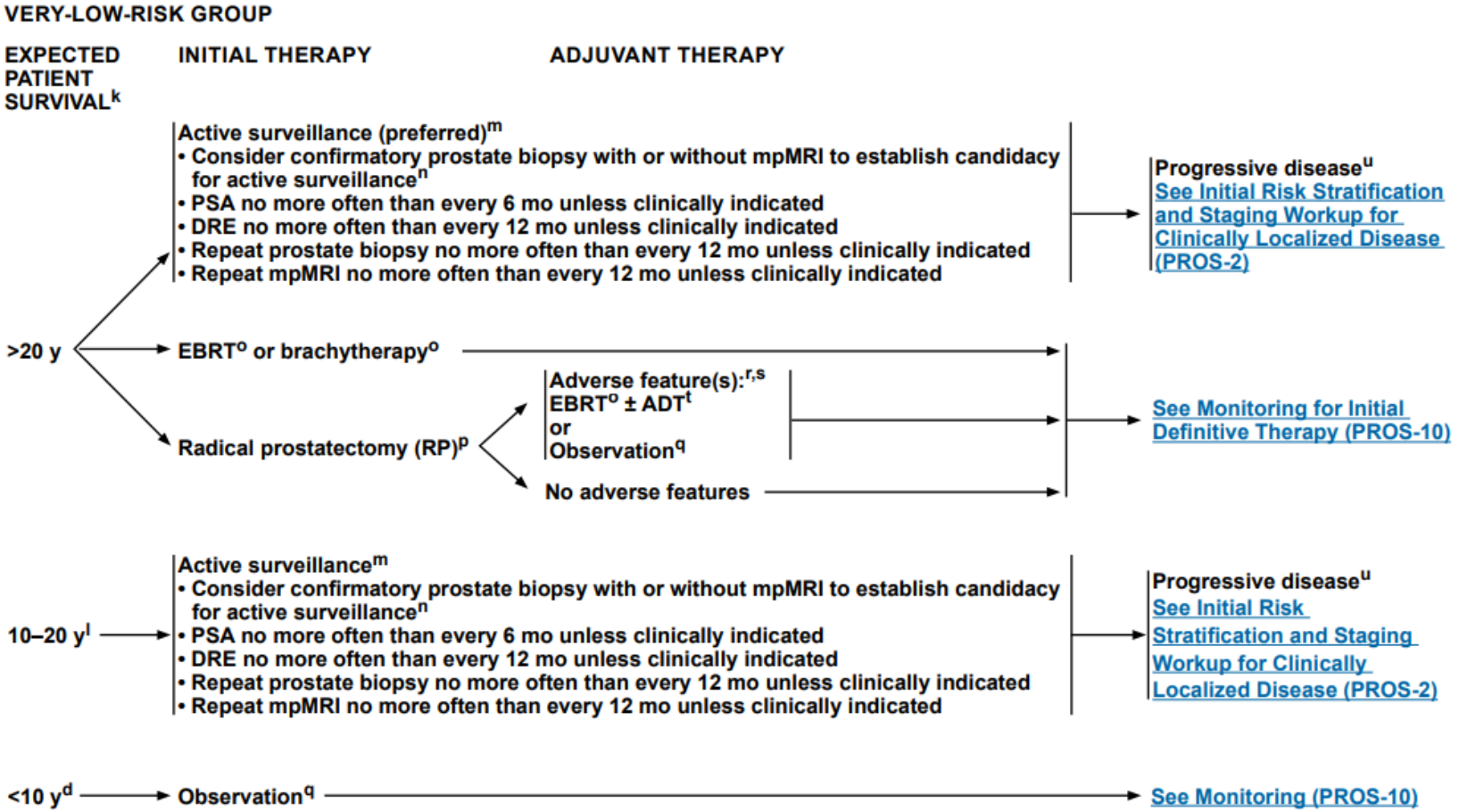
VERY-LOW-RISK GROUP



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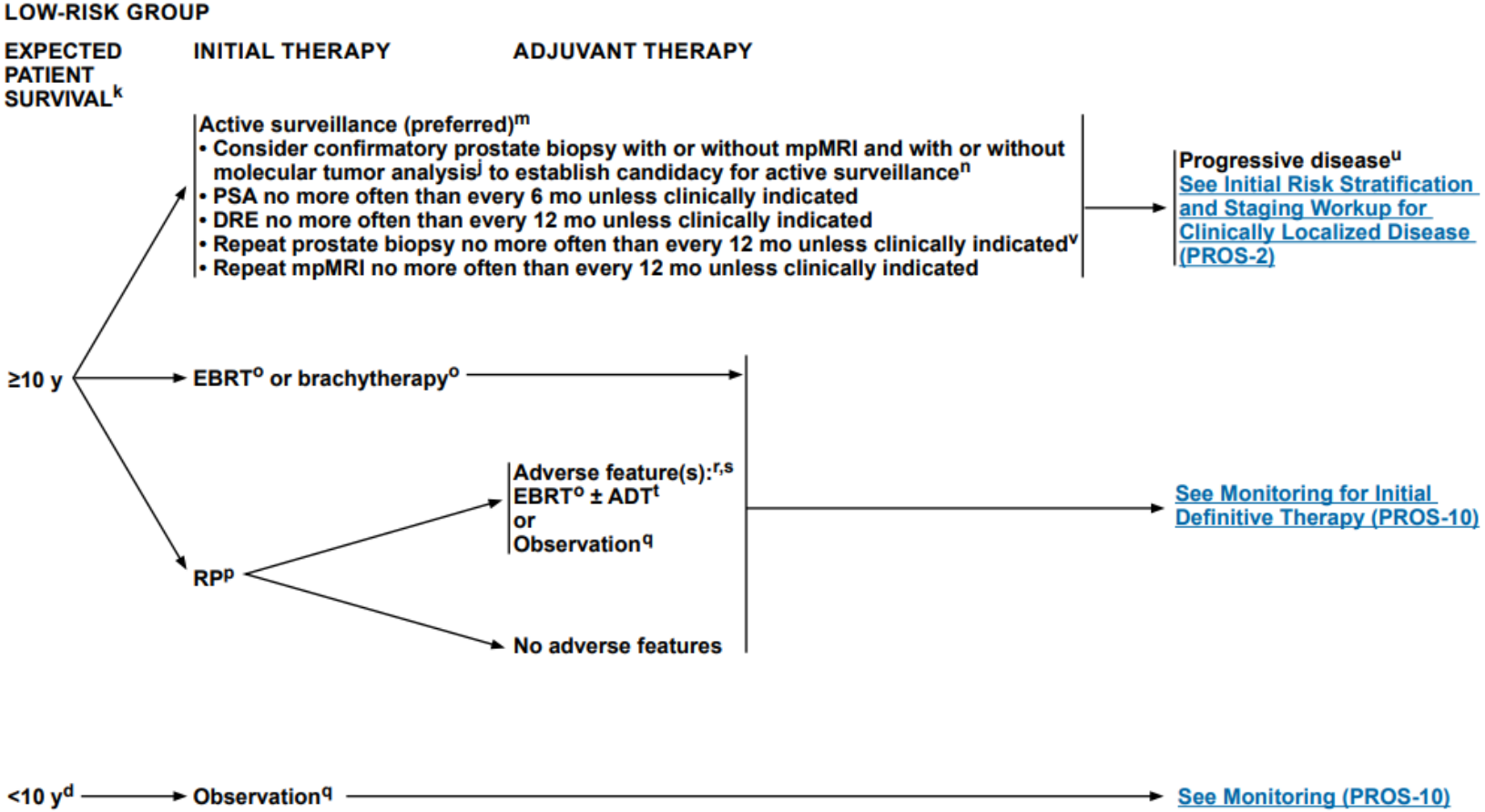


Active Surveillance

- Preferred for very low risk and low risk prostate cancer
- Typical AS regimen
  - mpMRI and confirmatory biopsy (ideally within 3-6 months)
  - PSA monitoring q 6 months
  - mpMRI/prostate biopsy q 18-24 months
- Advantages
  - Lower rates of bowel/bladder dysfunction, erectile dysfunction, urinary incontinence
- Disadvantages
  - Higher likelihood of progression to metastatic disease (6%)
  - Need for repeat biopsies with high-degree of patient non-compliance
  - High likelihood of progression necessitating additional treatment (30-50%)

Focal Therapy – Cryotherapy

- Transperineal cryotherapy probes placed in prostate under US guidance.
  - General anesthesia usually required
  - Urethral warming catheter placed to protect urethra
- Cell death occurs via 2 methods
  - Direct cellular injury secondary to dehydration / ice crystal formation within the cell
  - Stasis within the vasculature leads to necrosis secondary to ischemia
- Advantages
  - Minimally invasive, low down-time
  - Low rates of bowel/bladder dysfunction
- Disadvantages
  - Lack of prospective data to evaluate effectiveness
  - Risk of major complications such as rectourethral fistula

Focal Therapy – Cryotherapy

	Onik[17]	Ward[18***]	Bahn[19]	Lambert[20]	Ellis[21]
No. of Patients	48	1,160	73	25	60
Average Age (yrs)	N/A	68	64	68	69
Average Follow-up (yrs)	4.5	1.8	3.7	2.3	1.3
Gleason Score, No. of Patients (%)	N/A	≤ 6: 844 (74) 7: 240 (21) ≥ 8: 64 (6)	6: 30 (41) 7: 43 (59)	6: 13 (52) 7: 12 (48)	≤ 6: 47 (78.3) 7: 12 (20) ≥ 8: 1 (1.7)
Clinical Stage, No. of Patients (%)	N/A	≤ T2a: 1,013 (87) ≥ T2b: 147 (13)	T1c: 41 (56) T2a: 31 (43) T2b: 1 (1)	T1c: 25 (100)	≤ T2a: 55 (91.7) ≥ T2b: 5 (8.3)
Risk Category, No. of Patients (%)*	N/A	Low: 541 (47) Int: 473 (41) High: 143 (12)	Low: 24 (33) Int: 49 (67)	N/A	Low: 40 (66.7) Int: 14 (23.3) High: 6 (10)
Average PSA (ng/mL)**	Pre 7.8 Post 2.2	Pre 7.2 Post 2.15	Pre 5.9 Post 1.6	Pre 6.0 Post 2.4	Pre 7.2 Post 2.15
Biochemical Disease-free Survival (%)	94	74.7	75	85	80.4
Incontinence (%)	0	1.6	0	0	3.6
Potency Maintained (%)	90	58.1	86	71	70.6

Nguyen HD, Allen BJ, Pow-Sang JM. Focal cryotherapy in the treatment of localized prostate cancer. Cancer Control. 2013 Jul;20(3):177-80. doi: 10.1177/107327481302000305. PMID: 23811701.

Focal Therapy - HIFU

- Trans-rectal probe delivers parabolic focused ultrasound, typically under general anesthesia
- Thermal effect
  - US energy converted into heat
  - Causes tissue coagulation and leads to coagulative necrosis
- Mechanical effect
  - Negative pressure of US wave causes bubbles inside target cells which increase in size
  - High pressure develops when the bubbles suddenly collapse
- Often combined with a TURP to reduce post HIFU urethral sloughing and obstruction
- Advantages
  - Minimally invasive, low down-time
  - Low rates of bowel/bladder dysfunction
- Disadvantages
  - Lack of comparative prospective data to evaluate effectiveness
  - Existing body of evidence has insufficient long-term follow up

Chaussy CG, Thüroff S. High-Intensity Focused Ultrasound for the Treatment of Prostate Cancer: A Review. J Endourol. 2017 Apr;31(S1):S30-S37. doi: 10.1089/end.2016.0548. Epub 2017 Mar 29. PMID: 28355119.

Focal Therapy - HIFU

Table 4 – Clavien-Dindo classification of post-HIFU complications

Clavien-Dindo grade	Complication	Incidence, *n*/*N* (%)
I	Urinary tract infection	53/625 (8.5)
I	Epididymo-orchitis	12/625 (1.9)
IIIa	Rectourethral fistula	1/625 (0.2)
IIIb	Endoscopic procedures for LUTS	60/625 (9.6)
IIIb	Rectourethral fistula	1/625 (0.2)

HIFU = high-intensity focused ultrasound; LUTS = lower urinary tract symptoms.

Table 5 – Patient-reported outcome measure for urinary incontinence according to the EPIC urinary domain among men undergoing focal HIFU for nonmetastatic prostate cancer

Patient-reported urinary incontinence	Patients, *n* (%)	
	1–2 yr FU	2–3 yr FU
0 pads	304/313 (97)	241/247 (98)
0–1 pads	313/313 (100)	247/247 (100)
No leakage at all	208/250 (83)	156/195 (80)

EPIC = Expanded Prostate Cancer Index Composite; HIFU = high-intensity focused ultrasound; FU = follow-up.

Table 3 – Kaplan-Meier estimates of freedom from repeat HIFU, overall survival, metastasis-free survival, and overall failure-free survival following focal HIFU therapy among men treated for nonmetastatic prostate cancer

	Kaplan-Meier estimate, % (95% confidence interval)		
	1 yr	3 yr	5 yr
Overall survival	100 (99–100)	99 (98–100)	99 (97–100)
By D'Amico risk class			
Low	99 (96–100)	99 (96–100)	99 (96–100)
Intermediate	100 (99–100)	99 (98–100)	99 (97–100)
High	99.5 (98–100)	99 (97–100)	98 (96–100)
Metastasis-free survival	99.7 (99–100)	99 (98–100)	98 (97–99)
By D'Amico risk class			
Low	100 (NA)	99 (96–100)	96 (93–100)
Intermediate	99.7 (99–100)	99 (97–100)	99 (97–100)
High	99.5 (98–100)	98 (96–100)	97 (95–100)
Failure-free survival	99 (98–100)	92 (90–95)	88 (85–91)
By D'Amico risk class			
Low	99 (96–100)	96 (91–100)	96 (91–100)
Intermediate	99 (97–100)	93 (90–96)	88 (84–93)
High	98 (97–100)	89 (85–94)	84 (78–90)
By Gleason score			
≤6	99 (98–100)	95 (92–99)	92 (87–97)
7	99 (98–100)	92 (89–95)	87 (83–91)
≥8	89 (71–100)	89 (79–100)	59 (26–100)
By pre-HIFU PSA group			
<10 ng/ml	99.5 (99–100)	95 (93–97)	92 (89–95)
≥10 ng/ml	97 (94–100)	85 (78–91)	77 (69–84)
Free from repeat HIFU	98 (96–99)	84 (81–87)	75 (71–80)
By D'Amico risk class			
Low	97 (94–100)	82 (74–92)	78 (69–89)
Intermediate	97 (95–99)	88 (85–92)	79 (74–85)
High	98 (97–100)	76 (69–83)	68 (61–76)

HIFU = high-intensity focused ultrasound; NA = not applicable; PSA = prostate-specific antigen.

Guillaumier S, Peters M, Arya M, et al. A Multicentre Study of 5-year Outcomes Following Focal Therapy in Treating Clinically Significant Nonmetastatic Prostate Cancer. *Eur Urol*. 2018;74(4):422-429. doi:10.1016/j.eururo.2018.06.006

Surgery – Radical Prostatectomy

- 1st robot assisted laparoscopic radical prostatectomy
  - Frankfurt in 2000
- 1st large robotic series
  - Menon et al – Henry Ford Vattikuti Urology Institute
- Advances
  - Athermal dissection of neurovascular bundles
  - High release of lateral prostatic fascia
  - Rocco posterior reconstruction
  - Van Velt Hoven continuous urethro-vesical anastomosis
  - Extended pelvic lymph node dissection

Functional and Oncological Outcomes

- “Trifecta”
  - Potent
  - Continent
  - Negative surgical margins
- Partially surgeon / technique dependent
- Patient dependent
  - Extent of disease affects nerve and bladder neck sparing
  - Strong erections pre-op→ better potency post-op
- Technique dependent??
  - Conflicting data between open and robot assisted approaches

Functional and Oncological Outcomes

	6 months		12 months		24 months	
	Radical retropubic prostatectomy group (n=134)	Robot-assisted laparoscopic prostatectomy group (n=144)	Radical retropubic prostatectomy group (n=135)	Robot-assisted laparoscopic prostatectomy group (n=146)	Radical retropubic prostatectomy group (n=131)	Robot-assisted laparoscopic prostatectomy group (n=138)
Erections firm enough for intercourse*						
No sexual activity or almost never	76 (57%)	85 (59%)	69 (51%)	69 (47%)	58 (44%)	63 (46%)
Less than half the time or about half the time	28 (21%)	24 (17%)	25 (19%)	23 (16%)	25 (19%)	18 (13%)
More than half the time or almost always	29 (22%)	32 (22%)	40 (30%)	51 (35%)	47 (36%)	53 (38%)
Pad for incontinence†						
None	114 (85%)	121 (84%)	123 (91%)	131 (90%)	124 (95%)	126 (91%)
One pad per day	17 (13%)	18 (13%)	10 (7%)	14 (10%)	7 (5%)	9 (7%)
Two pads per day	3 (2%)	3 (2%)	1 (1%)	0 (0%)	0 (0%)	3 (2%)
Three or more pads per day	0 (0%)	1 (1%)	0 (0%)	1 (1%)	0 (0%)	0 (0%)

Data are n (%). Percentages might not sum to 100 because of rounding and missing data. *Erection quality generated from single International Index of Erectile Function item. †Use of pads generated from single Expanded Prostate Cancer Index Composite item.

Table 4: **Erectile function and pad use at 6 months, 12 months, and 24 months by surgery type**

Gardiner et al. Robot-assisted laparoscopic prostatectomy versus open radical retropubic prostatectomy: 24 month outcomes from a randomised controlled study. Lancet Oncology 2018: 19 1051-1060

Functional and Oncological Outcomes

	Radical retropubic prostatectomy group (n=151)	Robot-assisted laparoscopic prostatectomy group (n=157)
Progression		
Imaging evidence of progression	3 (2%)	1 (1%)
Biochemical recurrence	13 (9%)	4 (3%)
Additional treatment*		
Radiotherapy	10 (7%)	15 (10%)
Androgen deprivation therapy	4 (3%)	4 (3%)
Chemotherapy	1 (1%)	0 (0%)
At least one treatment	13 (9%)	16 (10%)

Data are n (%). Imaging evidence of progression test of equivalence p=0·2956; biochemical recurrence test of equivalence p=0·0199; at least one treatment χ^2 p=0·635. *Numbers of men who had additional treatments are not additive because some patients received more than one type.

***Table 2:* Oncological outcomes within 24 months by surgery type**

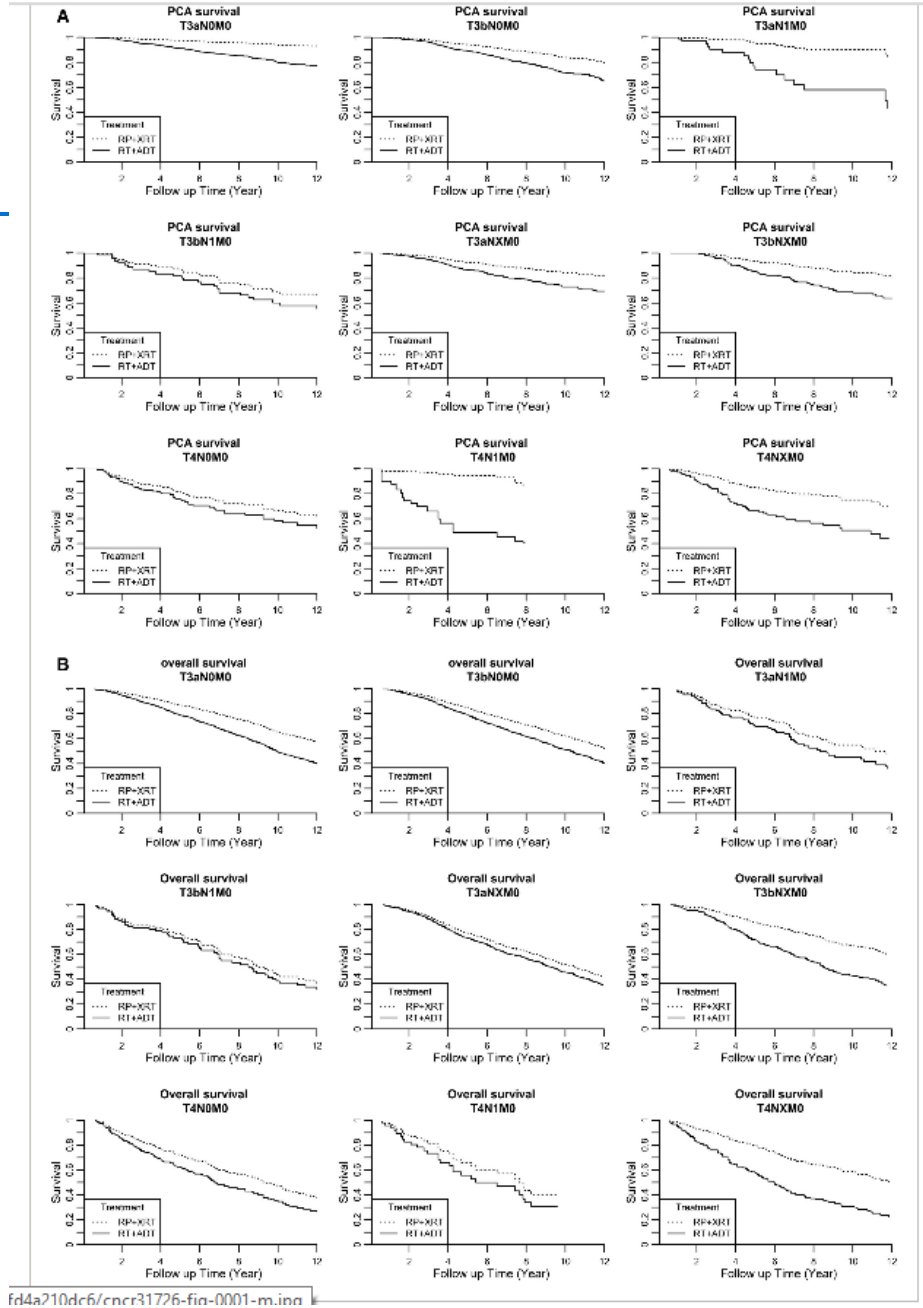
Gardiner et al. Robot-assisted laparoscopic prostatectomy versus open radical retropubic prostatectomy: 24 month outcomes from a randomised controlled study. Lancet Oncology 2018: 19 1051-1060

Surgery – Radical Prostatectomy

- Advantages
  - High cancer specific and overall survival
  - Allows for adjuvant radiation
- Disadvantages
  - Higher rates of incontinence / erectile dysfunction
  - Risk and recovery associated with major abdominal surgery

Surgery + Adjuvant Radiation

- SEER-Medicare data for cT3-4N0-1M0 prostate cancer
- Survival outcomes of prostatectomy plus XRT vs XRT plus ADT



Jang TL, Patel N, Faiena I, Radadia KD, Moore DF, Elsamra SE, Singer EA, Stein MN, Eastham JA, Scardino PT, Lin Y, Kim IY, Lu-Yao GL. Comparative effectiveness of radical prostatectomy with adjuvant radiotherapy versus radiotherapy plus androgen deprivation therapy for men with advanced prostate cancer. Cancer. 2018 Oct 15;124(20):4010-4022. doi: 10.1002/cncr.31726. Epub 2018 Sep 25. PMID: 30252932; PMCID: PMC6234085.

Radiation Options for Low or Favorable Intermediate Risk Prostate Cancer

- External beam radiation (EBRT) alone without hormonal therapy
  - Conventional course: 37-45 fractions at 1.8-2 Gy per fraction
  - Hypofractionated: 20-28 fractions at 2.5-3 Gy per fraction
  - SBRT: 5 fractions at 7.25-8 Gy per fraction

- Brachytherapy
  - Low Dose Rate (LDR) permanent implant – “seeds”: I-125 (145 Gy), Pd-103 (125 Gy), Cs-131 (115 Gy)
  - High Dose Rate (HDR) temporary implant: 13.5 Gy x 2 implants

Protect Trial

- The best comparative data for active surveillance, surgery, or EBRT (Phase 3 randomized)

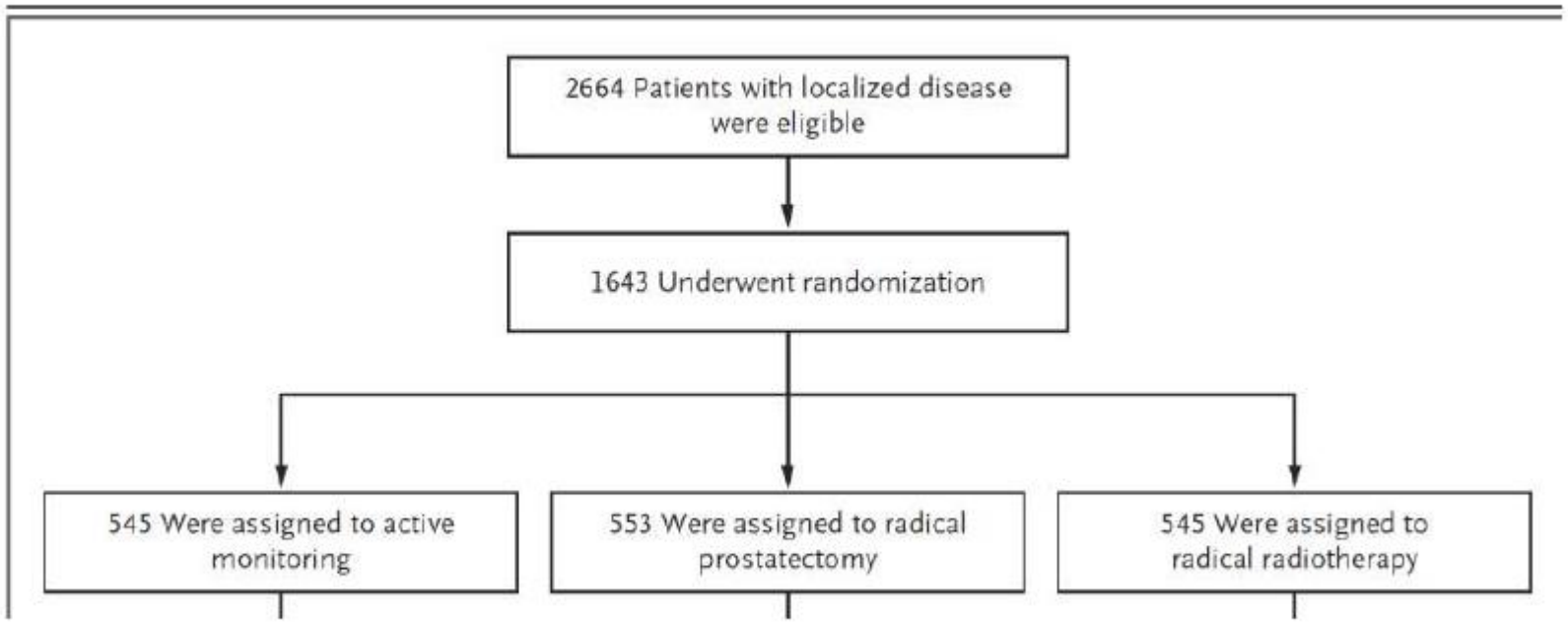
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 13, 2016 VOL. 375 NO. 15

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

F.C. Hamdy, J.L. Donovan, J.A. Lane, M. Mason, C. Metcalfe, P. Holding, M. Davis, T.J. Peters, E.L. Turner, R.M. Martin, J. Oxley, M. Robinson, J. Staffurth, E. Walsh, P. Bollina, J. Catto, A. Doble, A. Doherty, D. Gillatt, R. Kockelbergh, H. Kynaston, A. Paul, P. Powell, S. Prescott, D.J. Rosario, E. Rowe, and D.E. Neal, for the ProtecT Study Group*

Protect Trial



77% Gleason 6,
23% Gleason 7

Protect Trial

Half of AS Patients Get Treated by Yr 10

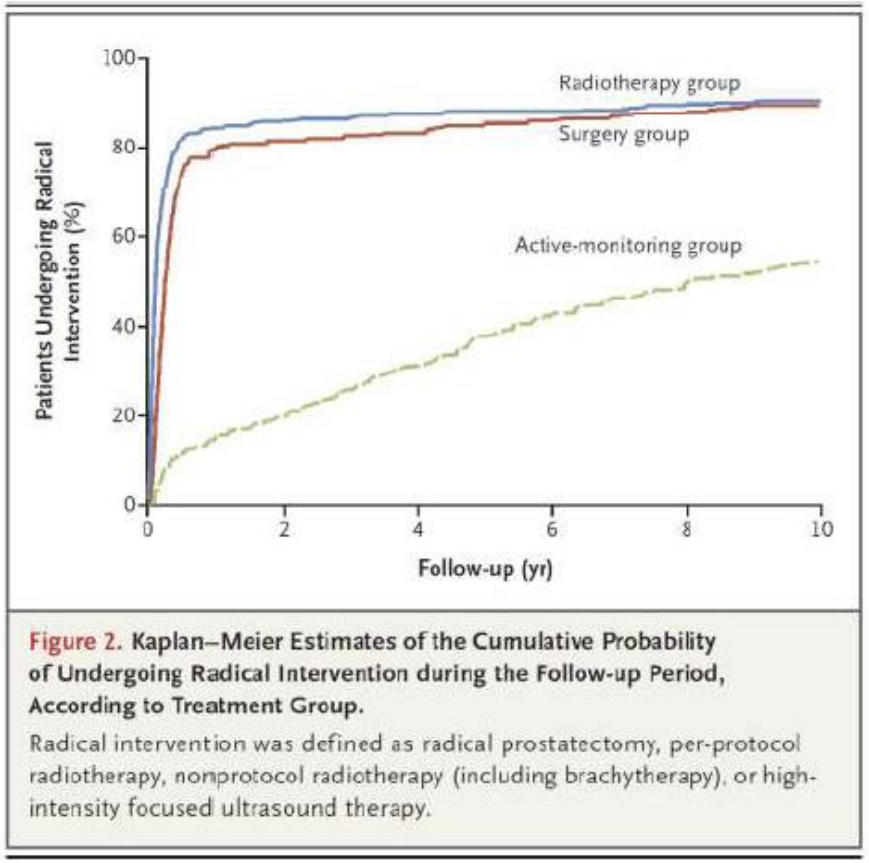


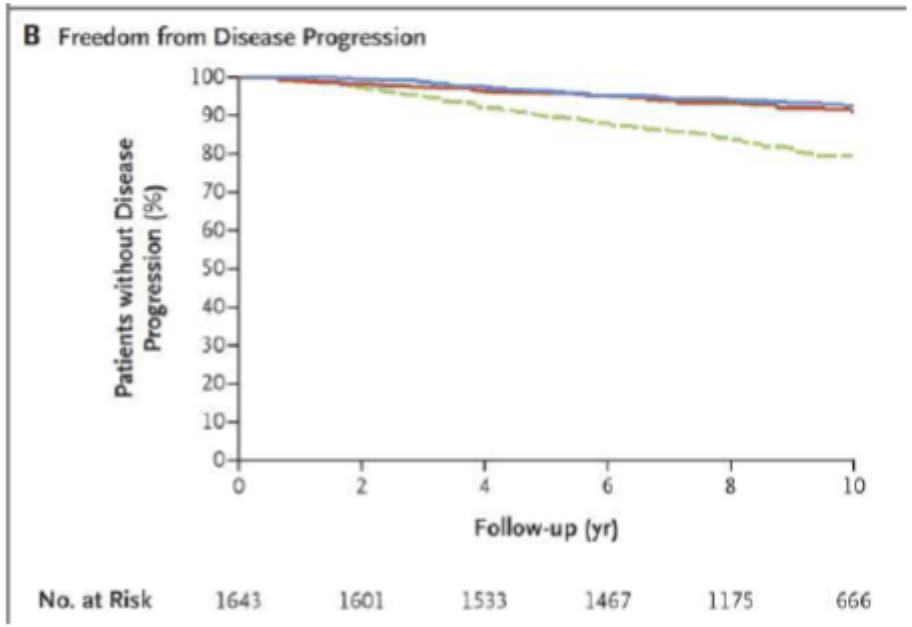
Figure 2. Kaplan–Meier Estimates of the Cumulative Probability of Undergoing Radical Intervention during the Follow-up Period, According to Treatment Group.

Radical intervention was defined as radical prostatectomy, per-protocol radiotherapy, nonprotocol radiotherapy (including brachytherapy), or high-intensity focused ultrasound therapy.

Protect Trial

- Driven by intermediate risk patients? NCCN/AUA/ASTRO allow AS for favorable intermediate risk patients but recommend it be used cautiously and after shared decision making

But more disease progression & Mets w/AS than with RT or RP



	Mets per 1000 person-years
Active Monitoring	6.3
Surgery	2.4
Radiation	3.0

Protect Trial

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	
[illegible]	[illegible]	[illegible]	[illegible]	
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

* P values were calculated with the use of a log-rank test of the null hypothesis of no difference in effectiveness across the three treatments. The planned adjusted analysis was not possible owing to the low number of events.
† Deaths due to prostate cancer were defined as deaths that were definitely or probably due to prostate cancer or its treatment, as determined by the independent cause-of-death evaluation committee.
‡ Disease progression was defined as death due to prostate cancer or its treatment; evidence of metastatic disease; long-term androgen-deprivation therapy; clinical T3 or T4 disease; and ureteric obstruction, rectal fistula, or the need for a permanent catheter when these are not considered to be a complication of treatment.

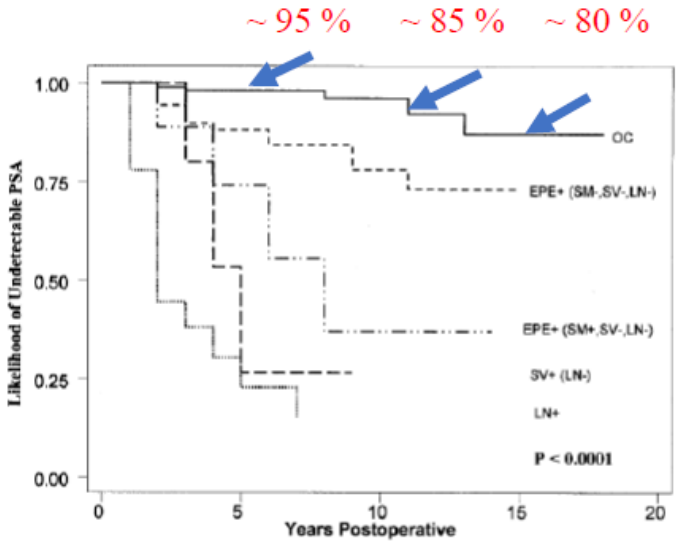
What about Brachytherapy?

Brachy Outcomes (Low-Risk)

Study	n	PSA control	F/U (yrs)	
Merrick	160	97 %	5	~ 95 %
Zelefsky	319	96 %	5	
Blasko	230	84 %	9	~ 85 %
Grimm	125	87 %	10	
Stone	279	78 %	10	
Potters	481	88 %	12	~ 80 %
Sylvester	215	86 %	15	

Merrick IJROBP 2001, Zelefsky IJROBP 2007, Blasko IJROBP 2000, Grimm IJROBP 2001, Stone J Urol 2005, Potters J Urol 2005,

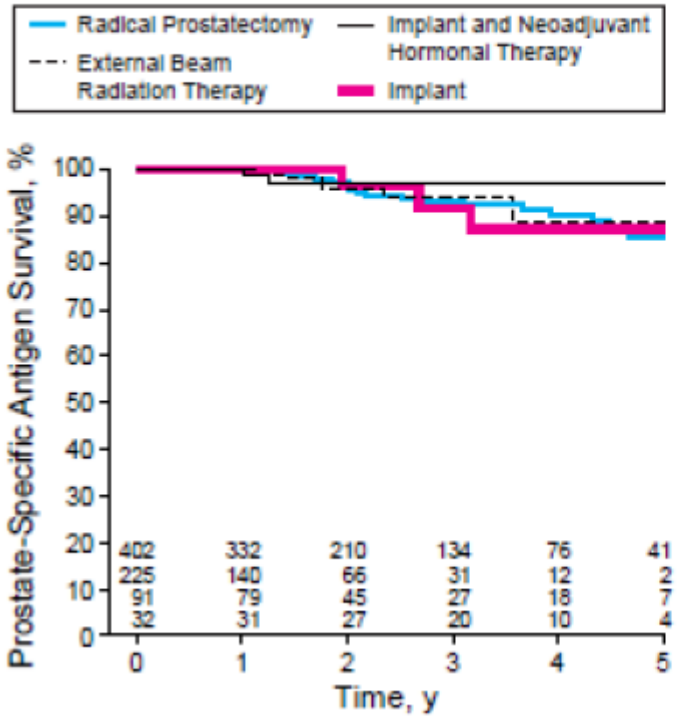
Johns Hopkins - Walsh @ 15 yrs RP Series



What about Brachytherapy?

Setting and Patients.—A total of 1872 men treated between January 1989 and October 1997 with an RP (n = 888) or implant with or without neoadjuvant androgen deprivation therapy (n = 218) at the Hospital of the University of Pennsylvania, Philadelphia, or RT (n = 766) at the Joint Center for Radiation Therapy, Boston, Mass, were enrolled.

All treatments have similar efficacy
D'Amico, JAMA 1998 – Low-Risk



- Low-Risk
  - cT1c-T2a
  - Gleason 6 or less
  - PSA<10
- RP, EBRT, Brachy had similar outcome

Which treatment is right for me?

- So if Prostatectomy, EBRT, and Brachytherapy all have comparable oncologic outcomes how should treatment decisions be made?
  - QoL/Toxicity
  - Treatment Logistics
  - Special considerations

Back to Protect

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

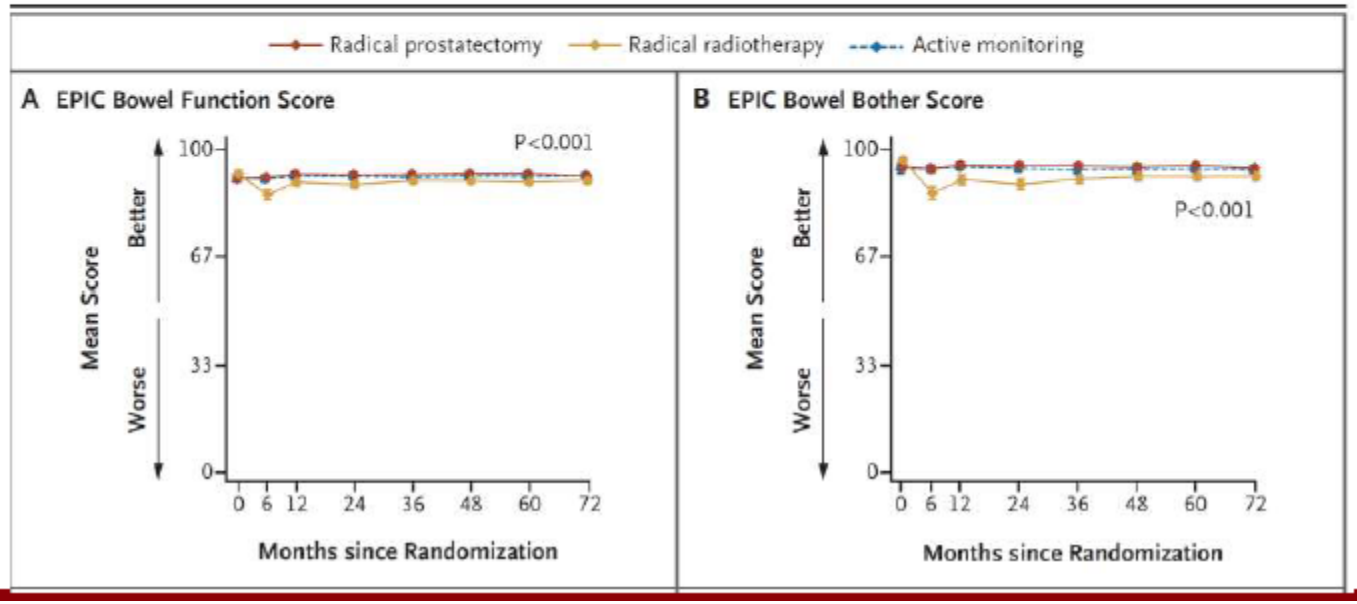
Patient-Reported Outcomes after Monitoring, Surgery, or Radiotherapy for Prostate Cancer

J.L. Donovan, F.C. Hamdy, J.A. Lane, M. Mason, C. Metcalfe, E. Walsh, J.M. Blazeby, T.J. Peters, P. Holding, S. Bonnington, T. Lennon, L. Bradshaw, D. Cooper, P. Herbert, J. Howson, A. Jones, N. Lyons, E. Salter, P. Thompson, S. Tidball, J. Blaikie, C. Gray, P. Bollina, J. Catto, A. Doble, A. Doherty, D. Gillatt, R. Kockelbergh, H. Kynaston, A. Paul, P. Powell, S. Prescott, D.J. Rosario, E. Rowe, M. Davis, E.L. Turner, R.M. Martin, and D.E. Neal, for the ProtecT Study Group*

Protect (randomized) QoL Data

Surgery Causes Fewer Bowel Symptoms Than RT

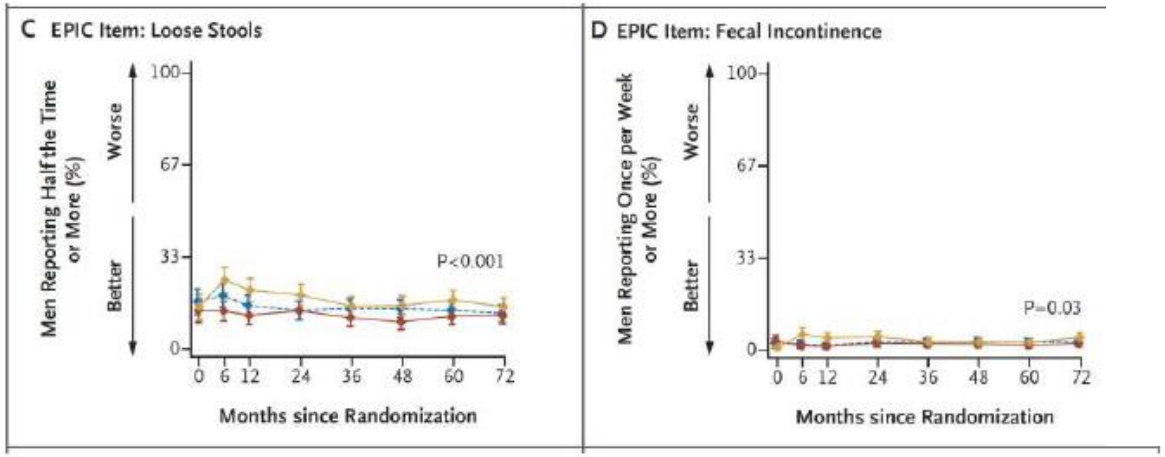
- Bowel Function and Bother



Protect (randomized) QoL Data

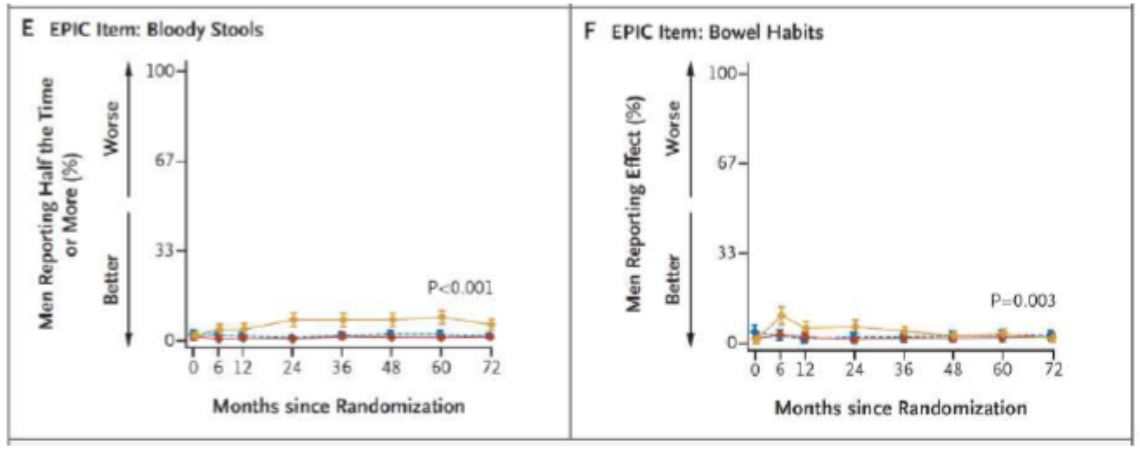
Surgery Causes Fewer Bowel Symptoms Than RT

- Loose Stools and Fecal Incontinence



Surgery Causes Fewer Bowel Symptoms Than RT

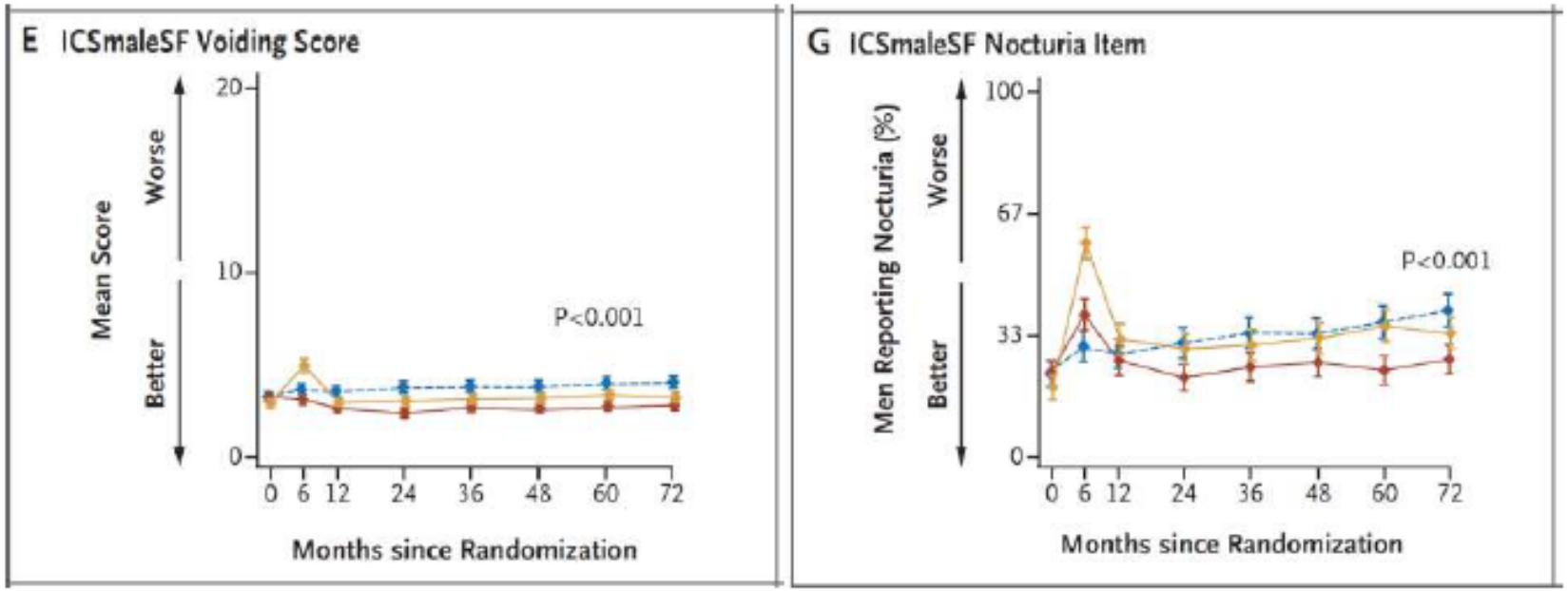
- Bloody Stools and Bowel Habits



Protect (randomized) QoL Data

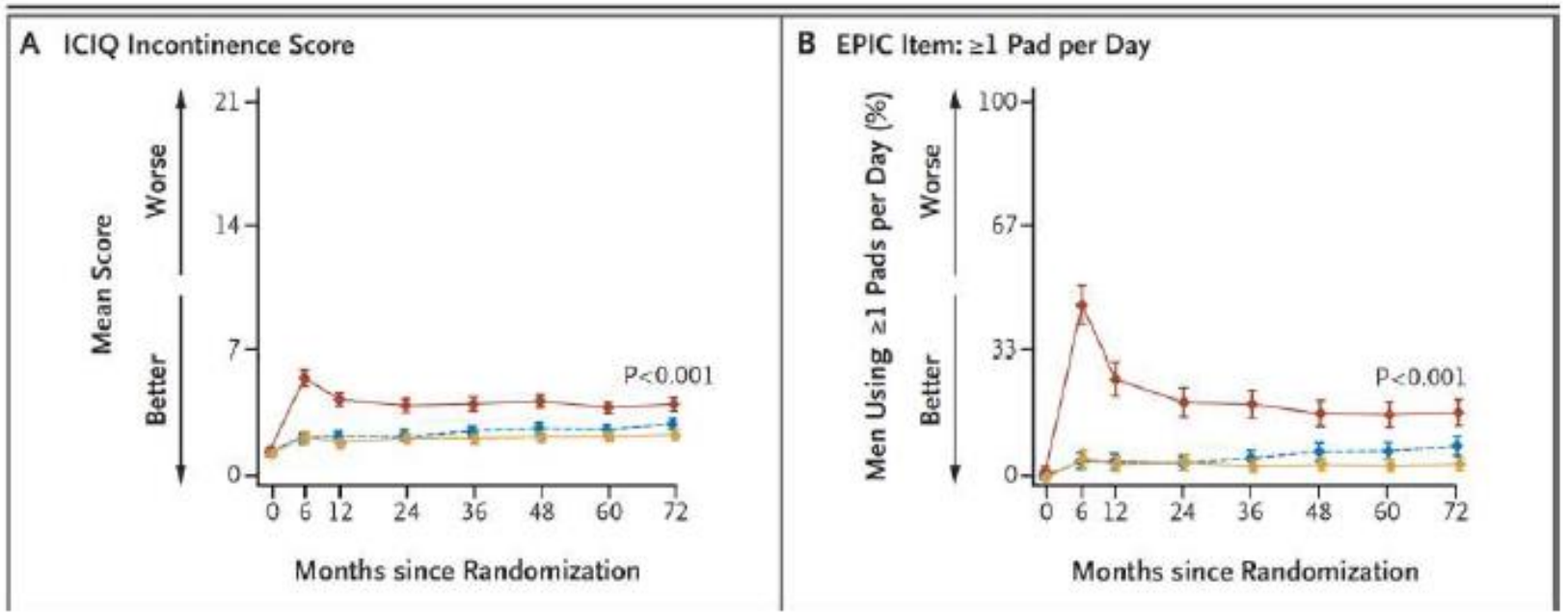
Surgery Had Fewer Obstructive Symptoms Than RT

- Voiding Score and Nocturia



Protect (randomized) QoL Data

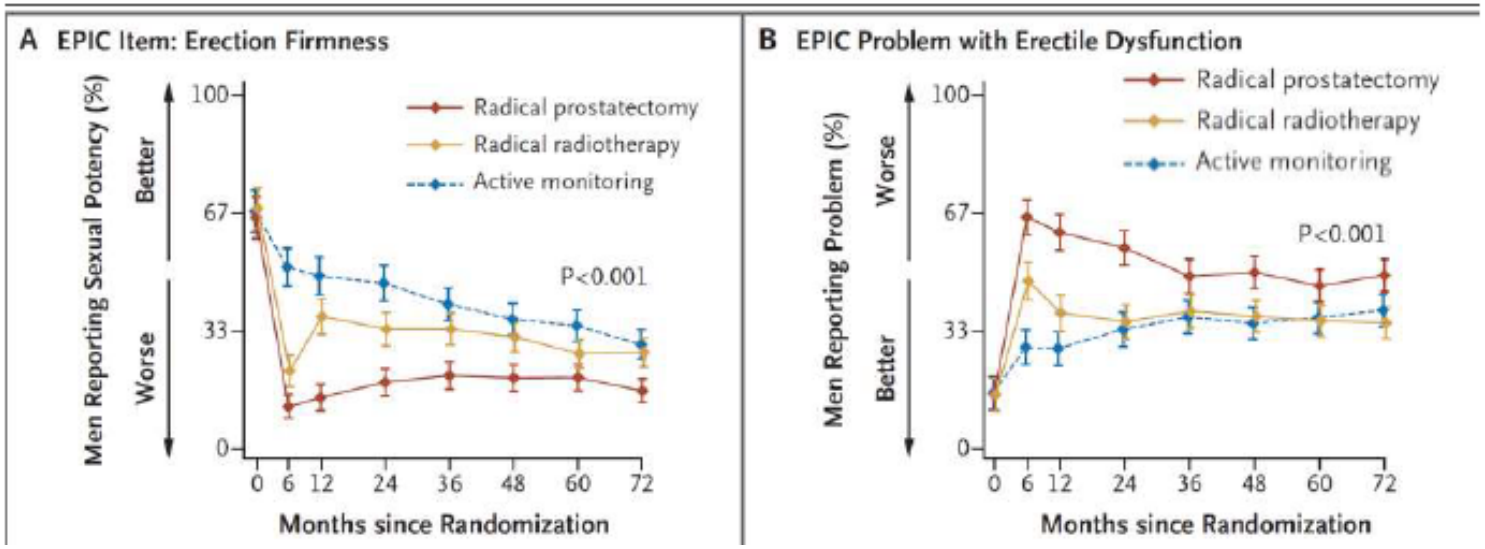
But RT Had Less Incontinence Than Surgery



Protect (randomized) QoL Data

And RT Had Better Erectile Function Than Surgery

- Erection Firmness and Erectile Dysfunction



Protect (randomized) QoL Data

Surgery v. RT+ADT QOL Facts

Symptom	Which Modality Better?
Erections	Radiation Better
Incontinence	Radiation Better
Urinary Obstructive Sxs	Surgery Better
Rectal problems	Surgery Better

What about brachytherapy?

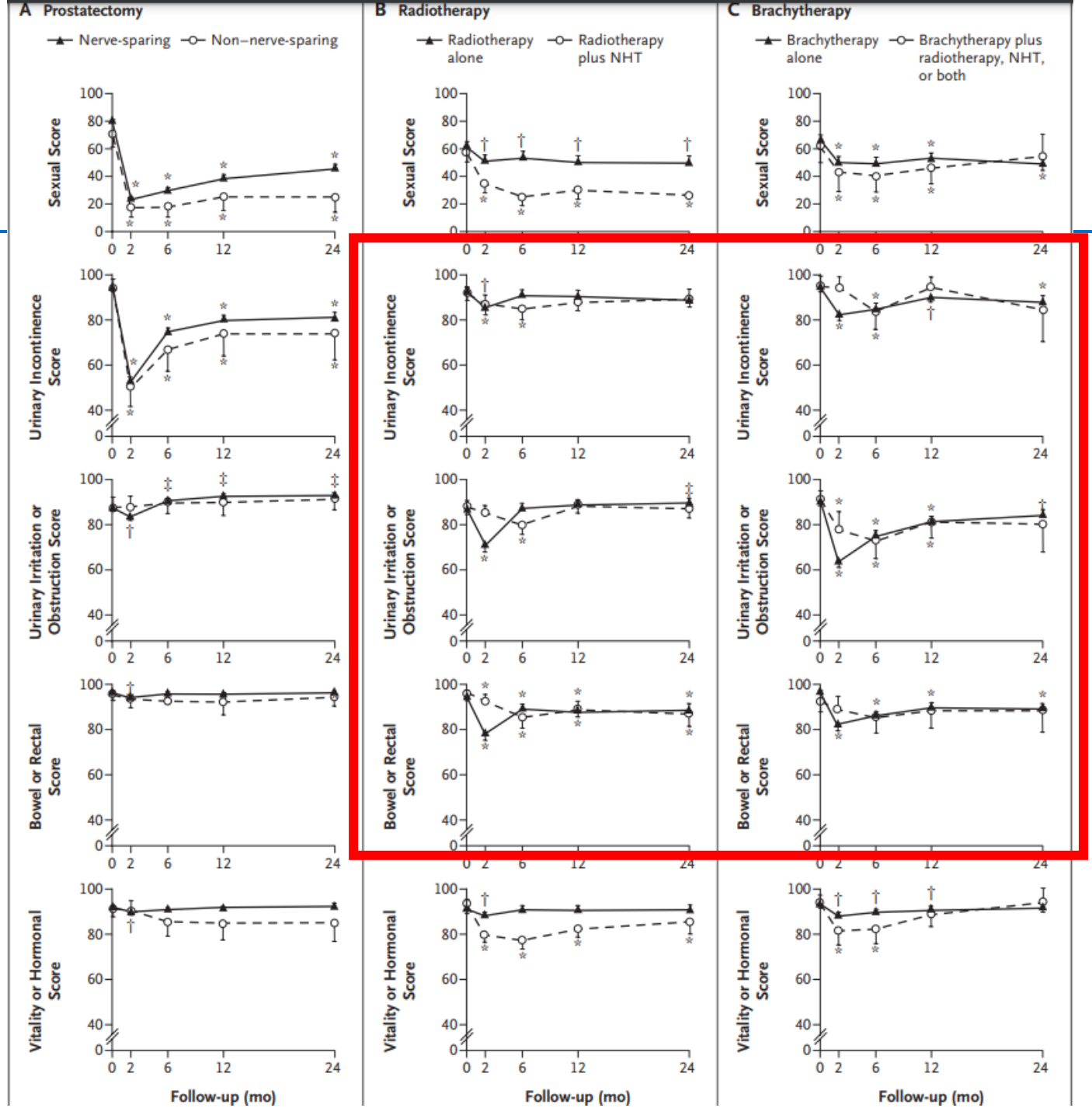
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Quality of Life and Satisfaction with Outcome among Prostate-Cancer Survivors

Martin G. Sanda, M.D., Rodney L. Dunn, M.S., Jeff Michalski, M.D., Howard M. Sandler, M.D., Laurel Northouse, R.N., Ph.D., Larry Hembroff, Ph.D., Xihong Lin, Ph.D., Thomas K. Greenfield, Ph.D., Mark S. Litwin, M.D., M.P.H., Christopher S. Saigal, M.D., M.P.H., Arul Mahadevan, M.D., Eric Klein, M.D., Adam Kibel, M.D., Louis L. Pisters, M.D., Deborah Kuban, M.D., Irving Kaplan, M.D., David Wood, M.D., Jay Ciezki, M.D., Nikhil Shah, D.O., and John T. Wei, M.D.

N Engl J Med 2008;358:1250-61.


A Prostatectomy
Nerve-sparing
Non–nerve-sparing
B Radiotherapy
Radiotherapy alone
Radiotherapy plus NHT
C Brachytherapy
Brachytherapy alone
Brachytherapy plus radiotherapy, NHT, or both
Sexual Score
Urinary Incontinence Score
Urinary Irritation or Obstruction Score
Bowel or Rectal Score
Vitality or Hormonal Score
Follow-up (mo)

SBRT

Original Investigation | Oncology

Long-term Outcomes of Stereotactic Body Radiotherapy for Low-Risk and Intermediate-Risk Prostate Cancer

Amar U. Kishan, MD; Audrey Dang, MD; Alan J. Katz, MD, JD; Constantine A. Mantz, MD; Sean P. Collins, MD, PhD; Nima Aghdam, MD; Fang-I Chu, PhD; Irving D. Kaplan, MD; Limor Appelbaum, MD; Donald B. Fuller, MD; Robert M. Meier, MD; D. Andrew Loblaw, MD; Patrick Cheung, MD; Huong T. Pham, MD; Narek Shaverdian, MD; Naomi Jiang, MD; Ye Yuan, MD, PhD; Hilary Bagshaw, MD; Nicolas Prionas, MD, PhD; Mark K. Buyyounouski, MD, MS; Daniel E. Spratt, MD; Patrick W. Linson, MD; Robert L. Hong, MD; Nicholas G. Nickols, MD, PhD; Michael L. Steinberg, MD; Patrick A. Kupelian, MD; Christopher R. King, MD, PhD

JAMA Network Open. 2019;2(2):e188006. doi:10.1001/jamanetworkopen.2018.8006

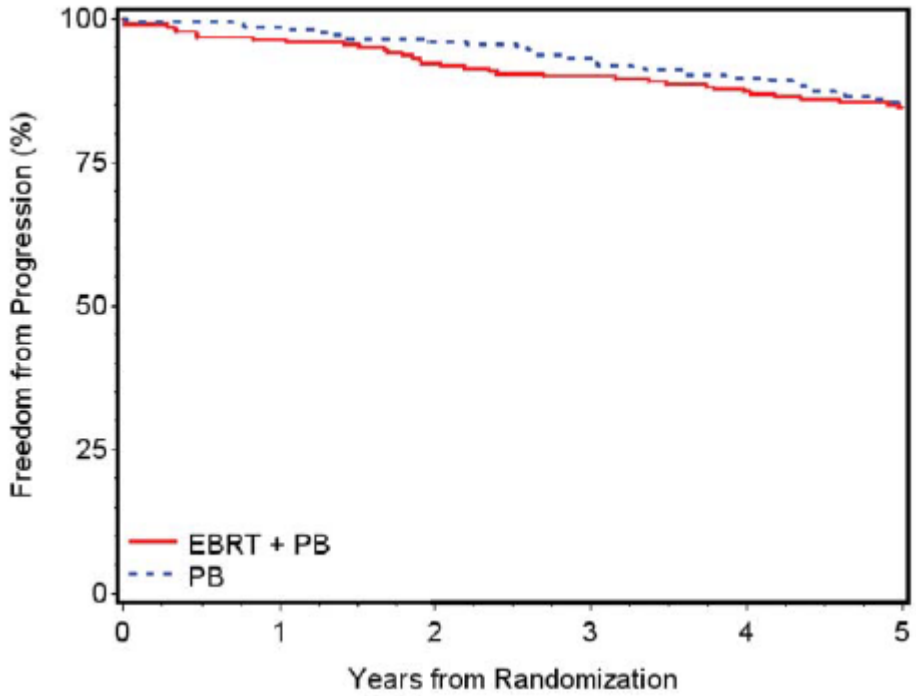
RESULTS A total of 2142 men (mean [SD] age, 67.9 [9.5] years) were eligible for analysis, of whom 1185 (55.3%) had low-risk disease, 692 (32.3%) had favorable intermediate-risk disease, and 265 (12.4%) had unfavorable intermediate-risk disease. The median follow-up period was 6.9 years (interquartile range, 4.9-8.1 years). Seven-year cumulative rates of biochemical recurrence were 4.5% (95% CI, 3.2%-5.8%) for low-risk disease, 8.6% (95% CI, 6.2%-11.0%) for favorable intermediate-risk disease, 14.9% (95% CI, 9.5%-20.2%) for unfavorable intermediate-risk disease, and 10.2% (95% CI, 8.0%-12.5%) for all intermediate-risk disease. The crude incidence of acute grade 3 or higher genitourinary toxic events was 0.60% (n = 13) and of gastrointestinal toxic events was 0.09% (n = 2), and the 7-year cumulative incidence of late grade 3 or higher genitourinary toxic events was 2.4% (95% CI, 1.8%-3.2%) and of late grade 3 or higher gastrointestinal toxic events was 0.4% (95% CI, 0.2%-0.8%).

EBRT+Brachy

- Not needed for favorable intermediate risk (just offer monotherapy)
- For higher risk patients 15-20% improvement in bPFS based on ASCENDE-RT randomized trial
  - Comes at cost of higher urinary toxicity

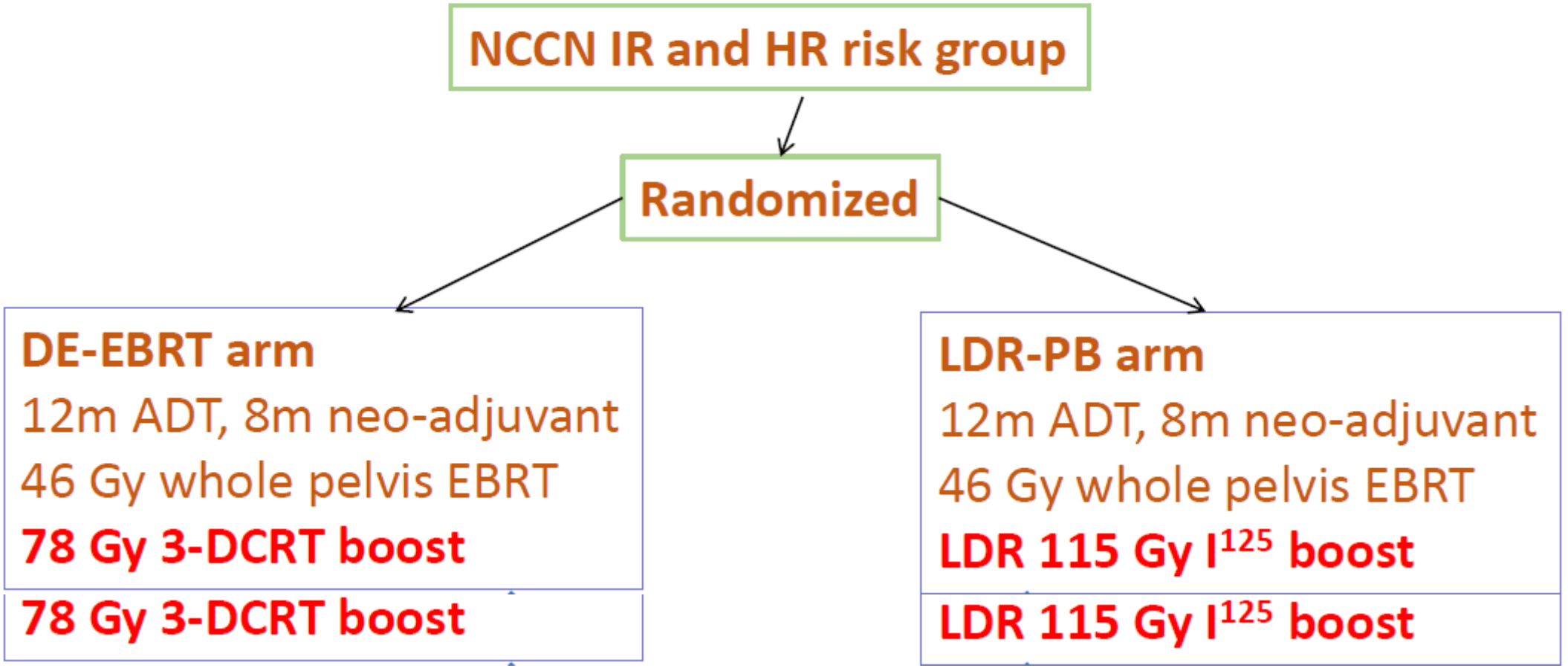
RTOG 0232 Eligibility Criteria

- Gleason score 2-6, and prostate-specific antigen ≥10 but < 20
- Gleason score 7, and prostate-specific antigen < 10



EBRT+Brachy

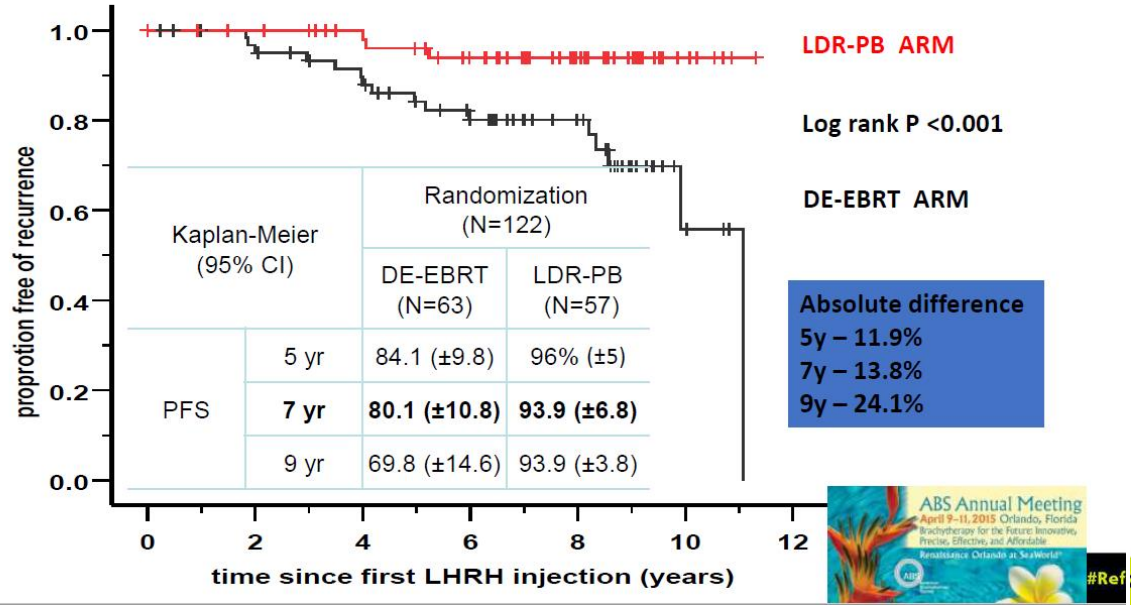
ASCENDE-RT



EBRT+Brachy

PFS by NCCN Risk Group
Intermediate-risk N=122

Morris/Keyes – BC Cancer Agency



Kaplan-Meier (95% CI)		Randomization (N=122) DE-EBRT (N=63)	LDR-PB (N=57)
PFS	5 yr	84.1 (±9.8)	96% (±5)
	7 yr	**80.1 (±10.8)**	**93.9 (±6.8)**
	9 yr	69.8 (±14.6)	93.9 (±3.8)

LDR-PB ARM

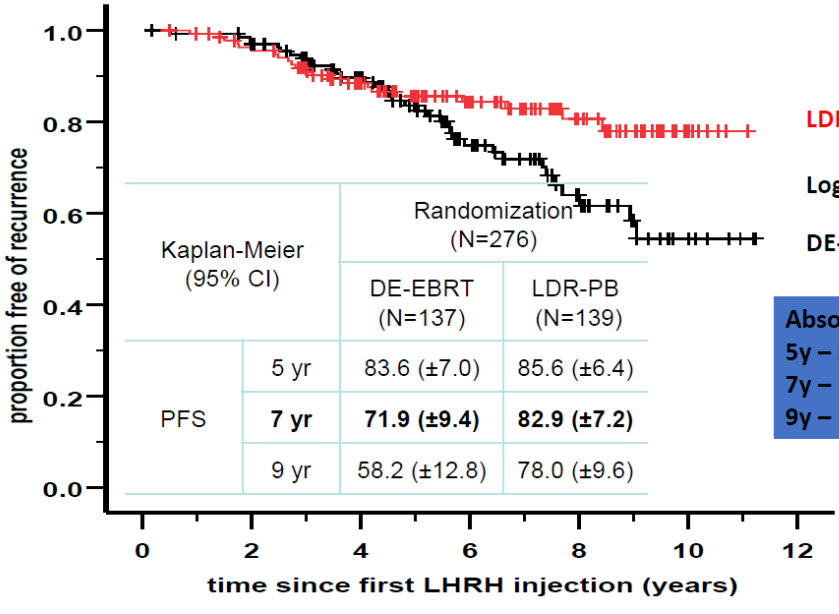
Log rank P <0.001

DE-EBRT ARM

Absolute difference
5y – 11.9%
7y – 13.8%
9y – 24.1%

PFS by NCCN Risk Group
High-Risk N=276

Morris/Keyes – BC Cancer Agency



Kaplan-Meier (95% CI)		Randomization (N=276) DE-EBRT (N=137)	LDR-PB (N=139)
PFS	5 yr	83.6 (±7.0)	85.6 (±6.4)
	7 yr	**71.9 (±9.4)**	**82.9 (±7.2)**
	9 yr	58.2 (±12.8)	78.0 (±9.6)

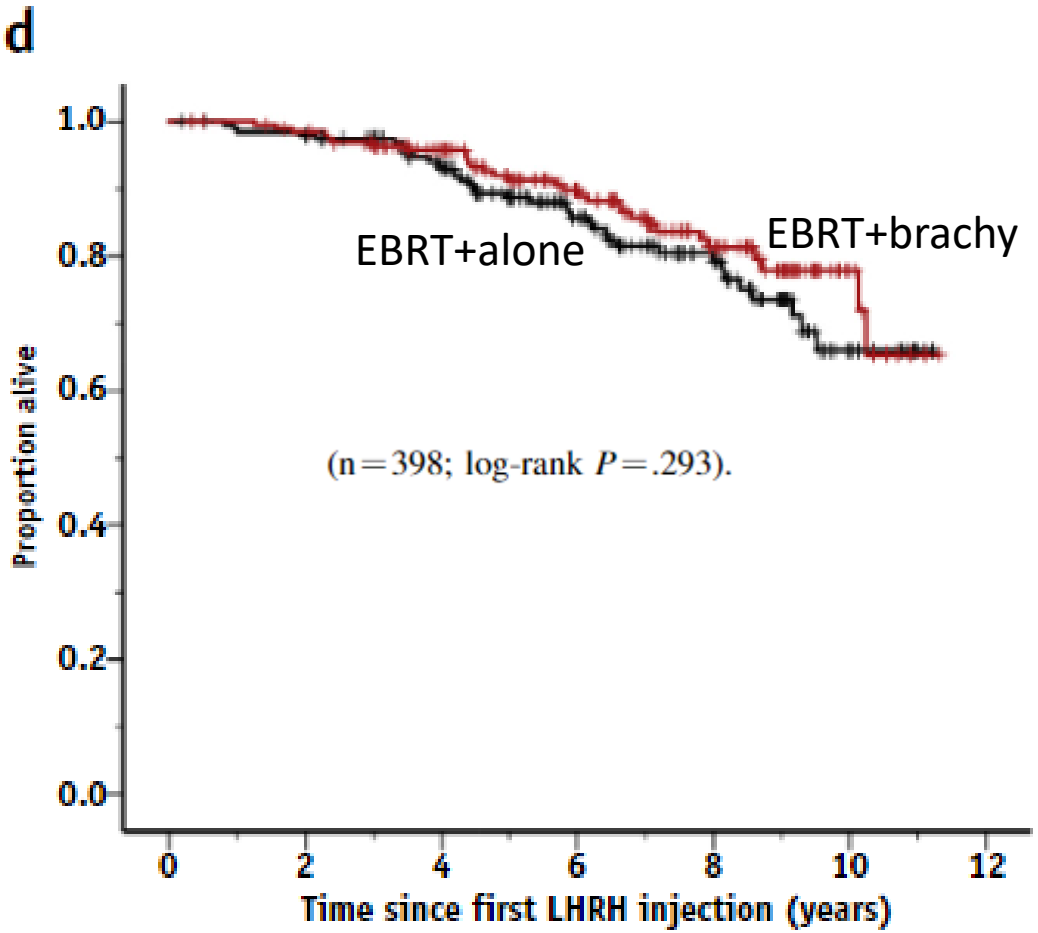
LDR-PB ARM

Log rank P = 0.05

DE-EBRT ARM

Absolute difference
5y – 2%
7y – 11.%
9y – 19.8%

EBRT+Brachy

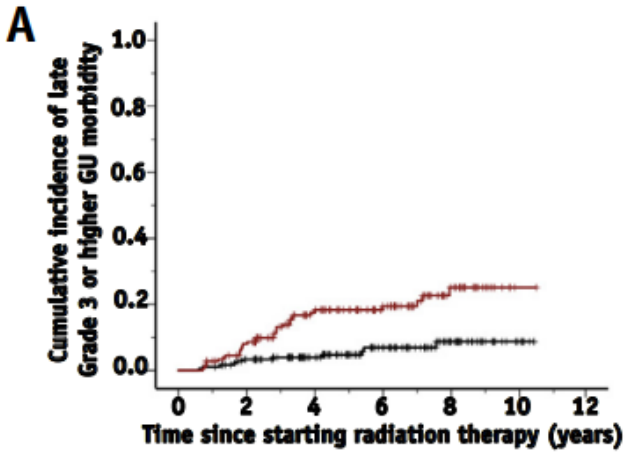

d
1.0
0.8
0.6
0.4
0.2
0.0
Proportion alive
EBRT+alone
EBRT+brachy
(n = 398; log-rank P = .293).
0
2
4
6
8
10
12
Time since first LHRH injection (years)

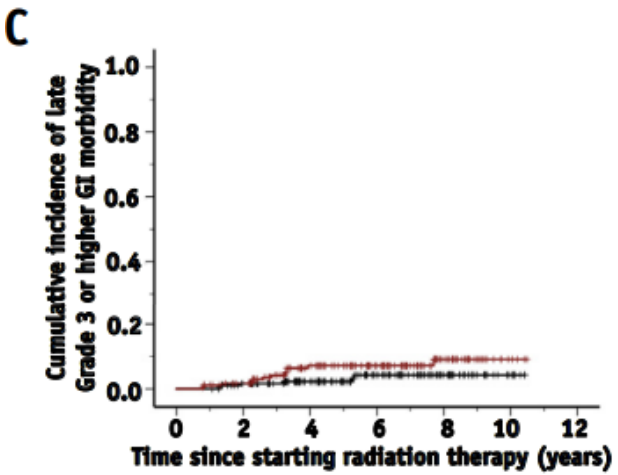
EBRT+Brachy

Table 4 Univariate and multivariable analysis (Cox model; backwards: conditional) for all-cause mortality

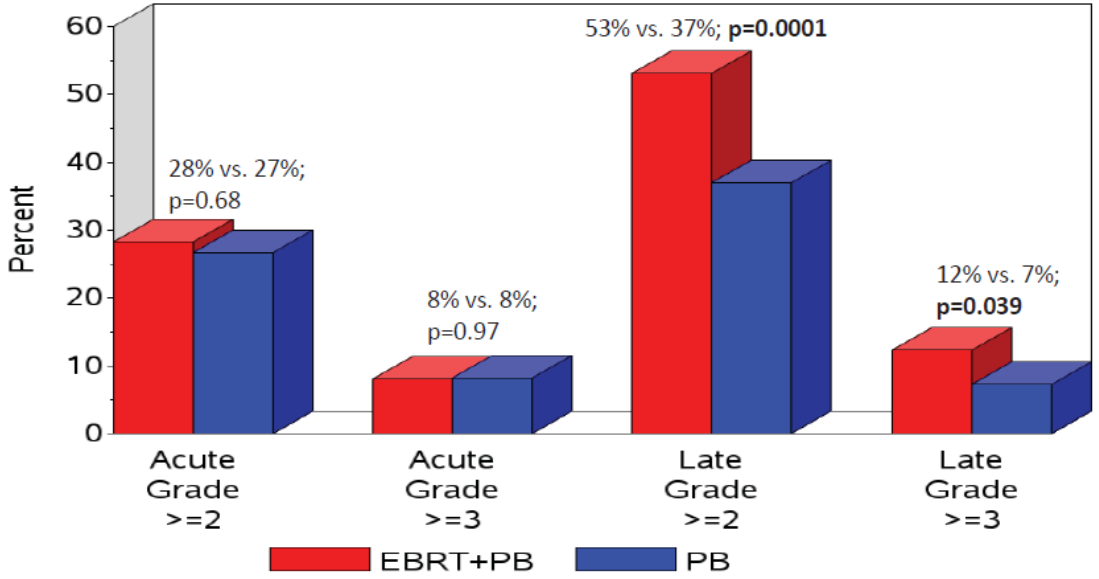
Variable	UVA			MVA Cox model		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Randomization arm*† (DE-EBRT vs LDR-PB)	1.29	0.80-2.08	.30	1.13	0.69-1.84	.62
PPC (unit = 1%)	1.00	0.99-1.01	.61	NA	NA	NA
Clinical T stage† (T3a vs T1-T2)	1.04	0.62-1.74	.89	NA	NA	NA
Log iPSA* (unit = 1 log)	1.28	0.86-1.89	.23	1.18	0.80-1.73	0.42
Risk code†‡ (high vs intermediate)	1.13	0.68-1.87	.64	NA	NA	NA
Number of high-risk features†‡ (≥3 vs ≤2)	1.30	0.68-2.49	.42	NA	NA	NA
Gleason sum† (8-10 vs ≤7)	1.23	0.76-2.01	.40	NA	NA	NA
Age* (unit = 1 y)	**1.05**	**1.02-1.09**	**.004**§	**1.05**	**1.02-1.09**	**.006**§
Disease status*‖ (relapse vs no relapse)	**6.60**	**3.80-11.4**	**<.001**§	**6.30**	**3.62-10.9**	**<.001**§

EBRT+Brachy





Results: Adverse Events



Unfavorable Intermediate Risk

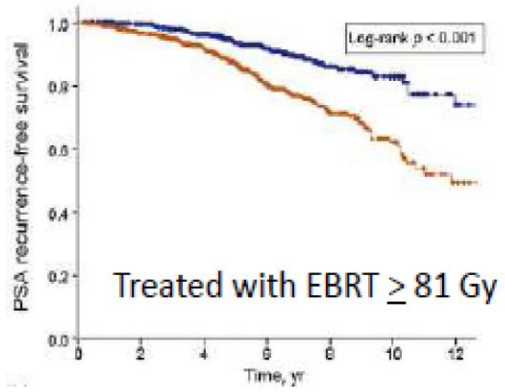
- Treatment Paradigm
  - RP
  - Radiation
    - Short course ADT recommended (4-6 months)
    - SBRT still an option
    - Brachytherapy monotherapy used selectively
    - Consideration of combo EBRT+Brachy

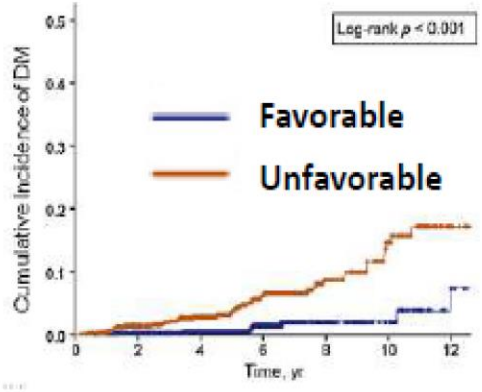
Unfavorable Intermediate Risk

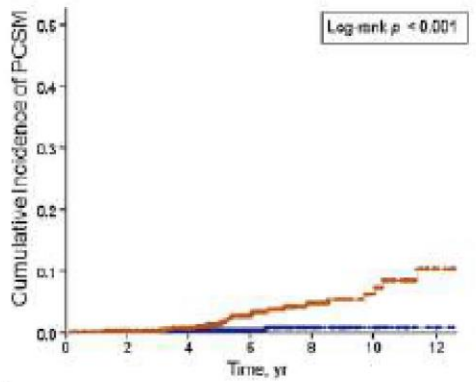
Intermediate-risk prostate cancer is a heterogeneous disease

- Unfavorable intermediate-risk: Gleason pattern 4+3=7, ≥ 50% biopsy cores, or multiple intermediate risk factors
- Favorable intermediate-risk: all others

PSA recurrence free survival	Cumulative incidence DM	Cumulative incidence PCSM







Zumsteg European Urology 2013 62:895

Unfavorable Intermediate Risk

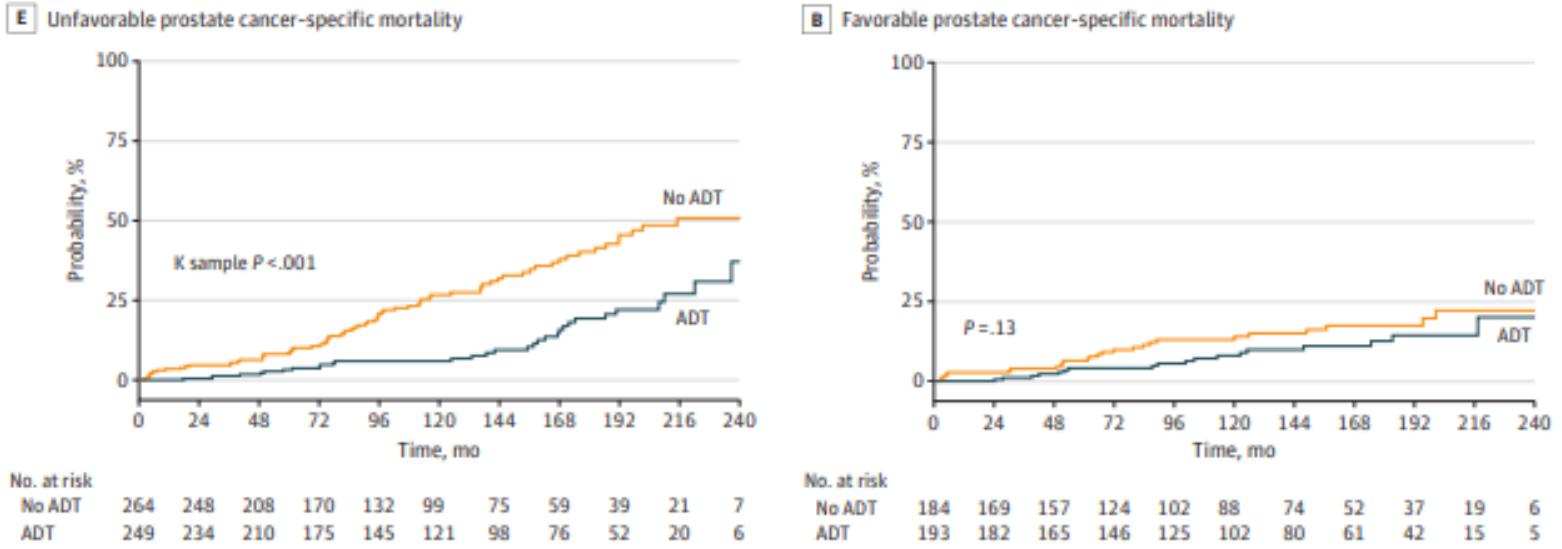
Research Letter | Oncology

Effect of Androgen Deprivation on Long-term Outcomes of Intermediate-Risk Prostate Cancer Stratified as Favorable or Unfavorable
A Secondary Analysis of the RTOG 9408 Randomized Clinical Trial

Zachary S. Zumsteg, MD; Daniel E. Spratt, MD; Timothy J. Daskivich, MD; Mourad Tighiouart, PhD; Michael Luu, MPH; Joseph P. Rodgers, MS; Howard M. Sandler, MD

JAMA Network Open. 2020;3(9):e2015083. doi:10.1001/jamanetworkopen.2020.15083

Figure. Outcomes for Patients With Favorable Intermediate-Risk or Unfavorable Intermediate-Risk Prostate Cancer Undergoing Radiation With or Without Androgen Deprivation Therapy (ADT)



High Risk

- Treatment Paradigm
  - RP
  - Radiation
    - Long course ADT recommended (18 months)
    - SBRT allowed by NCCN in select cases but minimal data and many radiation oncologists avoid or offer on protocol
    - Brachytherapy monotherapy avoided
    - Consideration of combo EBRT+Brachy

Duration of ADT for High Risk Patients

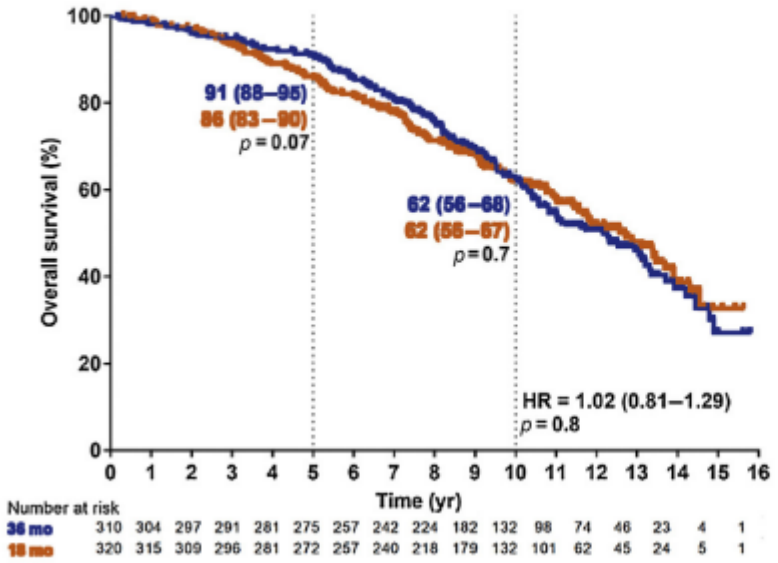
Duration of Androgen Deprivation Therapy in High-risk Prostate Cancer: A Randomized Phase III Trial

EUROPEAN UROLOGY 74 (2018) 432–441

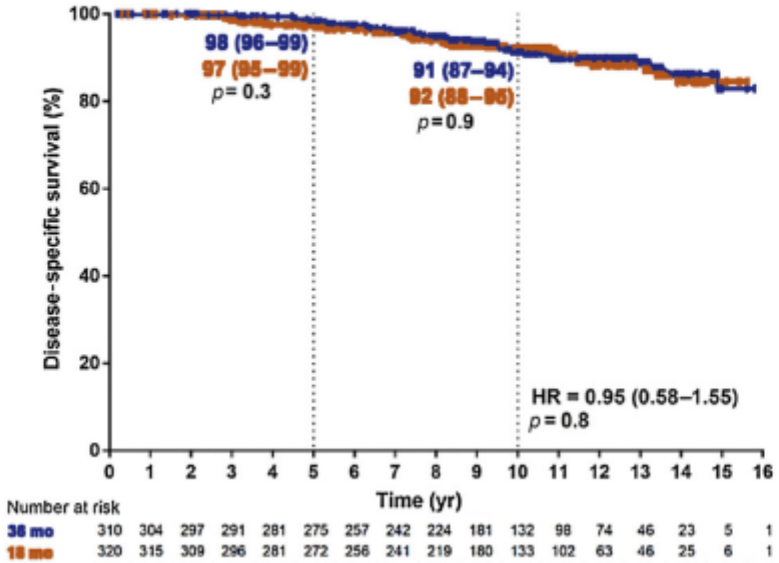
Abdenour Nabid [a,], Nathalie Carrier [a], André-Guy Martin [b], Jean-Paul Bahary [c], Céline Lemaire [d], Sylvie Vass [e], Boris Bahoric [f], Robert Archambault [g], François Vincent [h], Redouane Bettahar [i], Marie Duclos [j], Marie-Pierre Garant [a], Luis Souhami [j]*

- Randomized to 18 vs 36 months ADT

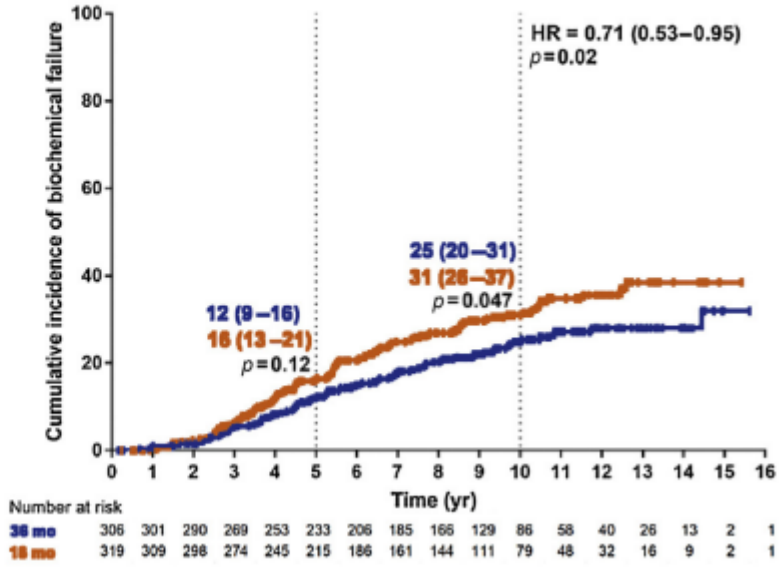
A Overall survival



B Disease-specific survival



C Biochemical failure



Summary

		Risk Group			
		Low	Fav Int	Unfav Int	High
Treatment	Prostatectomy	x	x	x	x
	EBRT Alone	x	x		
	Brachy Alone	x	x		
	SBRT Alone	x	x		
	SBRT + ADT			x	
	XRT+ADT			x	x
	XRT+Brachy+ADT			x	x

- Active Surveillance preferred for low risk and can be considered in select favorable intermediate risk

Summary

			Logistics / QoL				
		Anesthesia	Short Tx	Favorable bowel tox	Less Incontinenece	Less Urinary Irritation	No ADT	Erectile Function
Treatment	Prostatectomy							
	EBRT Alone							
	Brachy Alone							
	SBRT Alone							
	SBRT + ADT							
	XRT+ADT							
	XRT+Brachy+ADT							

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