

XXXII CONGRESSO NAZIONALE AIRO
XXXIII CONGRESSO NAZIONALE AIRB
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AIRO2022

Radioterapia di precisione per un'oncologia innovativa e sostenibile

BOLOGNA, 25-27 NOVEMBRE
PALAZZO DEI CONGRESSI

Il paziente giovane con tumore della prostata: Chirurgia, Radioterapia e strategie di intensificazione della dose

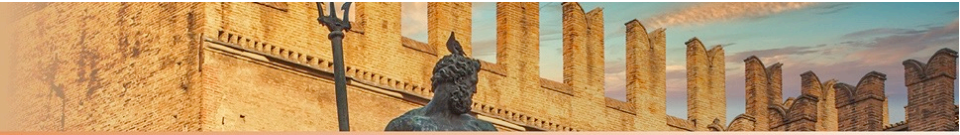
*Andrea Lancia,
Fondazione IRCCS Policlinico San Matteo,
Pavia*



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DISCLOSURE

No Conflicts of Interest to declare



Prostate Cancer: How Young is too Young?

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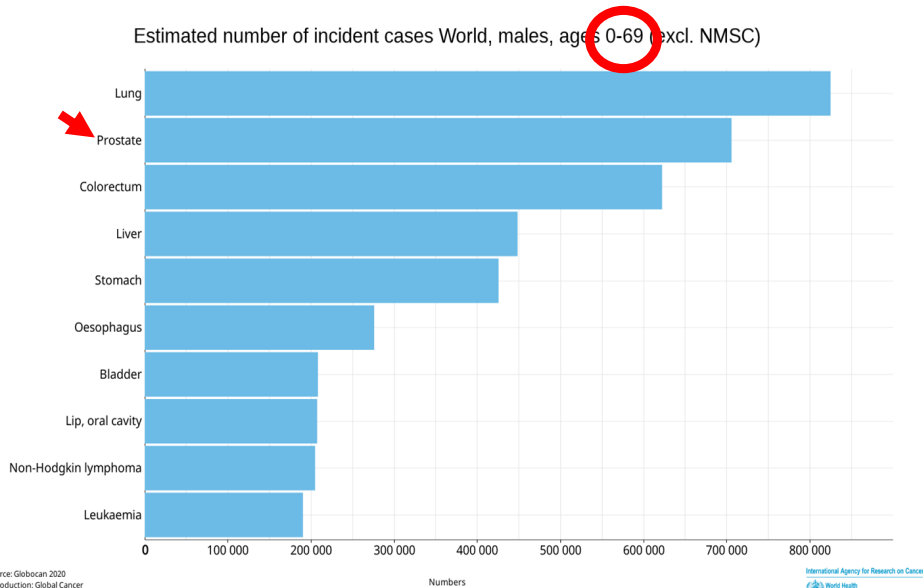


TABLE 4. Probability (%) of Developing Invasive Cancers Within Selected Age Intervals by Sex, United States, 2006 to 2008*

		BIRTH TO 39	40 TO 59	60 TO 69	70 AND OLDER	BIRTH TO DEATH
All sites†	Male	1.45 (1 in 69)	8.68 (1 in 12)	16.00 (1 in 6)	38.27 (1 in 3)	44.85 (1 in 2)
	Female	2.15 (1 in 46)	9.10 (1 in 11)	10.34 (1 in 10)	26.68 (1 in 4)	38.08 (1 in 3)
Urinary bladder‡	Male	0.02 (1 in 5,035)	0.38 (1 in 266)	0.92 (1 in 109)	3.71 (1 in 27)	3.84 (1 in 26)
	Female	0.01 (1 in 12,662)	0.12 (1 in 851)	0.25 (1 in 400)	0.98 (1 in 102)	1.15 (1 in 87)
Breast	Female	0.49 (1 in 203)	3.76 (1 in 27)	3.53 (1 in 28)	6.58 (1 in 15)	12.29 (1 in 8)
	Male	0.08 (1 in 1,265)	0.92 (1 in 109)	1.44 (1 in 70)	4.32 (1 in 23)	5.27 (1 in 19)
Colorectum	Female	0.08 (1 in 1,268)	0.73 (1 in 137)	1.01 (1 in 99)	3.95 (1 in 25)	4.91 (1 in 20)
	Male	0.16 (1 in 618)	0.22 (1 in 445)	0.34 (1 in 291)	1.24 (1 in 81)	1.57 (1 in 64)
Leukemia	Male	0.14 (1 in 733)	0.15 (1 in 665)	0.21 (1 in 482)	0.81 (1 in 123)	1.14 (1 in 88)
	Female	0.03 (1 in 3,631)	0.91 (1 in 109)	2.26 (1 in 44)	6.69 (1 in 15)	7.66 (1 in 13)
Lung & bronchus	Female	0.03 (1 in 3,205)	0.76 (1 in 132)	1.72 (1 in 58)	4.91 (1 in 20)	6.33 (1 in 16)
	Male	0.15 (1 in 673)	0.63 (1 in 158)	0.75 (1 in 133)	1.94 (1 in 52)	2.80 (1 in 36)
Melanoma of the skin§	Female	0.27 (1 in 371)	0.56 (1 in 180)	0.39 (1 in 256)	0.82 (1 in 123)	1.83 (1 in 55)
	Male	0.13 (1 in 775)	0.45 (1 in 223)	0.60 (1 in 167)	1.77 (1 in 57)	2.34 (1 in 43)
Non-Hodgkin lymphoma	Female	0.09 (1 in 1,155)	0.32 (1 in 313)	0.44 (1 in 228)	1.41 (1 in 71)	1.94 (1 in 51)
	Male	0.01 (1 in 8,499)	2.63 (1 in 38)	6.84 (1 in 15)	12.54 (1 in 8)	16.48 (1 in 6)
Prostate	Male	0.01 (1 in 8,499)	2.63 (1 in 38)	6.84 (1 in 15)	12.54 (1 in 8)	16.48 (1 in 6)
Uterine cervix	Female	0.15 (1 in 650)	0.27 (1 in 373)	0.13 (1 in 771)	0.18 (1 in 549)	0.68 (1 in 147)
Uterine corpus	Female	0.07 (1 in 1,373)	0.77 (1 in 130)	0.87 (1 in 114)	1.24 (1 in 81)	2.61 (1 in 38)

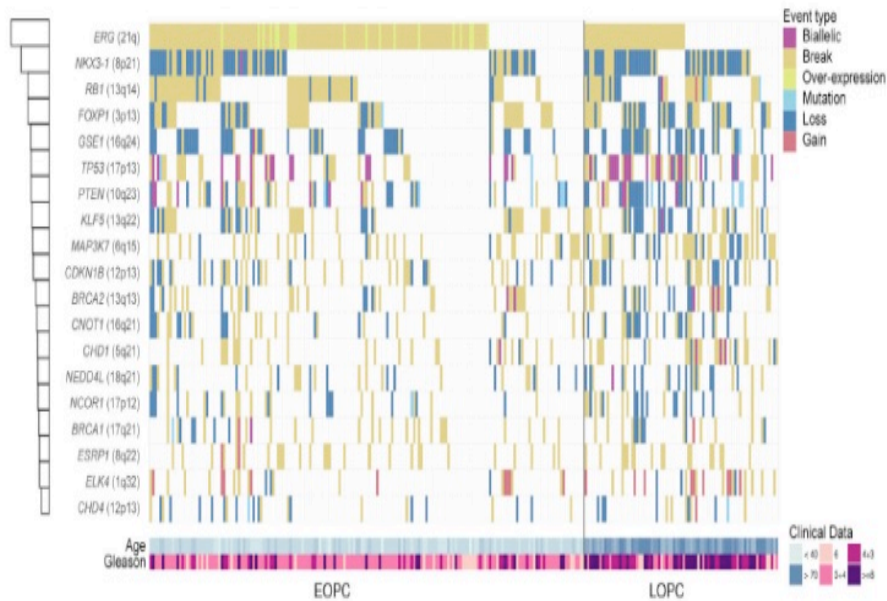
Sun H, GLOBOCAN 2020

Siegel R, Cancer Statistics 2012



Early Onset Prostate Cancer Has A Significant Genetic Component

Ethan M. Lange,^{1,2,3} Claudia A. Salinas,^{4*} Kimberly A. Zuhlke,⁴ Anna M. Ray,⁴
 Yunfei Wang,^{1,2} Yurong Lu,¹ Lindsey A. Ho,² Jingchun Luo,³ and
 Kathleen A. Cooney^{4,5,6}



- The incidence of prostate cancer in young men (aged ≤ 55 years) has increased sharply over the past two decades, making early-onset prostate cancer an important emerging issue for public health
- Increased screening in young men could account for some, but not all, of the increase in incidence of early-onset prostate cancer
- Advanced-stage and high-grade early-onset prostate cancer might be a distinct clinicopathological subtype with more rapid progression to disease-specific death than late-onset prostate cancer of similar stage and grade
- Men with early-onset prostate cancer tend to have a greater genetic risk than their older peers, making this group an ideal resource for investigating genetic susceptibility to prostate cancer



JAMA Oncology | Original Investigation

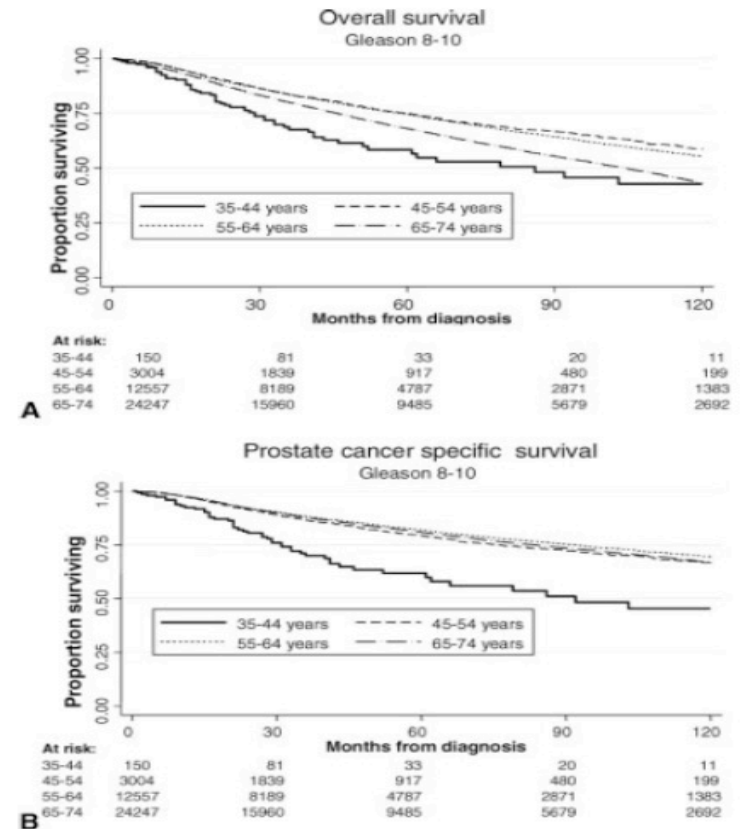
Development and Validation of a Clinical Prognostic Stage Group System for Nonmetastatic Prostate Cancer Using Disease-Specific Mortality Results From the International Staging Collaboration for Cancer of the Prostate

Robert T. Dess, MD; Krithika Suresh, PhD; Michael J. Zelefsky, MD; Stephen J. Freedland, MD; Brandon A. Mahal, MD; Matthew R. Cooperberg, MD, MPH; Brian J. Davis, MD, PhD; Eric M. Horwitz, MD; Martha K. Terris, MD; Christopher L. Amling, MD; William J. Aronson, MD; Christopher J. Kane, MD; William C. Jackson, MD; Jason W. D. Hearn, MD; Curtiland Deville, MD; Theodore L. DeWeese, MD; Stephen Greco, MD; Todd R. McNutt, MS, PhD; Daniel Y. Song, MD; Yilun Sun, PhD; Rohit Mehra, MD; Samuel D. Kaffenberger, MD; Todd M. Morgan, MD; Paul L. Nguyen, MD; Felix Y. Feng, MD; Vidit Sharma, MD; Phuoc T. Tran, MD, PhD; Bradley J. Stish, MD; Thomas M. Pisansky, MD; Nicholas G. Zaorsky, MD; Fabio Ynoe Moraes, MD; Alejandro Berlin, MD, MSc; Antonio Finelli, MD; Nicola Fossati, MD; Giorgio Gandaglia, MD; Alberto Briganti, MD; Peter R. Carroll, MD; R. Jeffrey Karnes, MD; Michael W. Kattan, PhD; Matthew J. Schipper, PhD; Daniel E. Spratt, MD

Table 2. Fine-Gray Regression Model of Prostate Cancer-Specific Mortality in Training Cohort

Training cohort	No. (%) of patients	Coefficient (SE)	sHR (95% CI)	P value	Points ^a
Age, y					
≤50	445 (4.5)	0.44 (0.38)	1.55 (0.74-3.24)	.24	1
>50 to 70	7286 (73.5)	NA	1 [Reference]	NA	0
>70 to 100	2184 (22.0)	0.27 (0.16)	1.32 (0.97-1.79)	.08	1

Dess RT, Jama Oncol, 2020

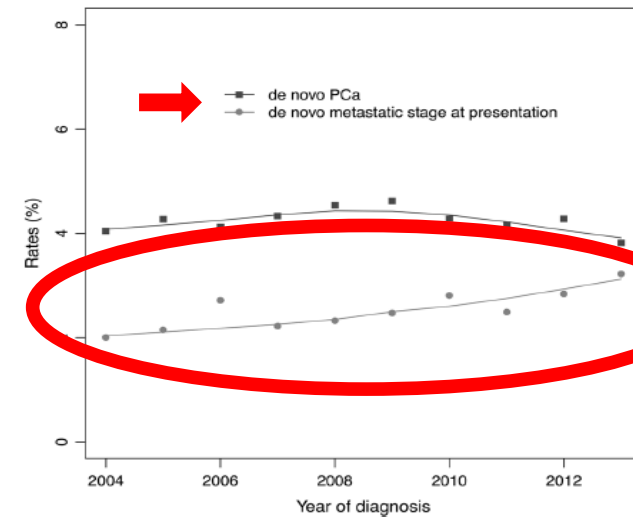
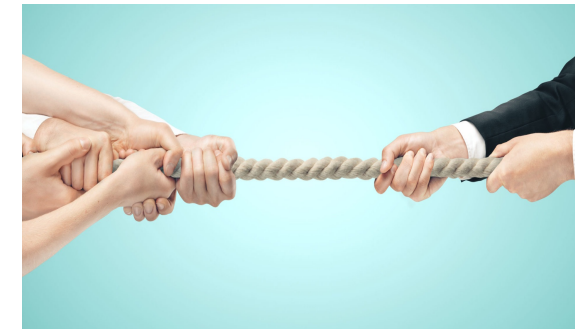
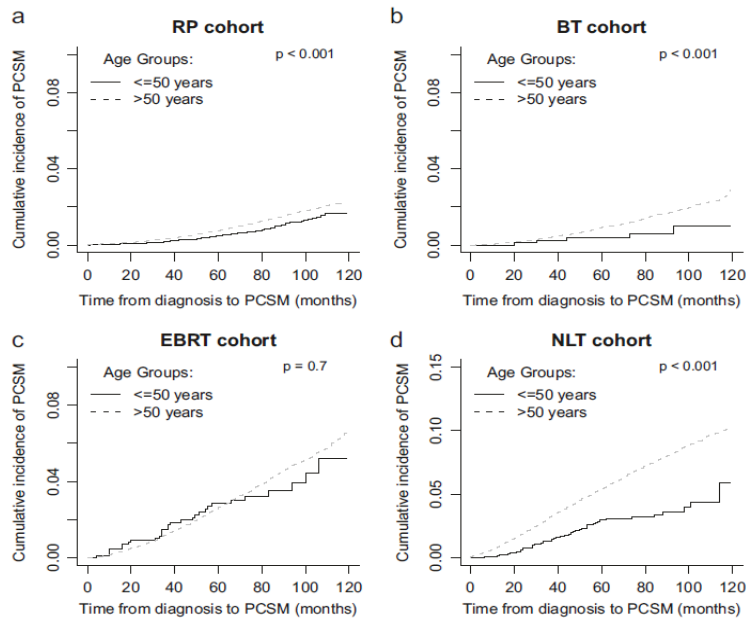


Lin DW, Cancer, 2009



Tumor characteristics, treatments, and oncological outcomes of prostate cancer in men aged ≤ 50 years: a population-based study

Raisa S. Pompe^{1,2} · Ariane Smith^{2,3} · Marco Bandini^{2,4} · Michele Marchioni^{2,5} · Tristan Martel^{2,3} · Felix Preisser¹ · Sami-Ramzi Leyh-Bannurah^{1,2,6} · Jonas Schiffmann⁷ · Fred Saad^{2,3} · Hartwig Huland¹ · Markus Graefen¹ · Shahrokh F. Shariat⁸ · Derya Tilki^{2,6} · Pierre I. Karakiewicz^{2,3}



$P=0.004$

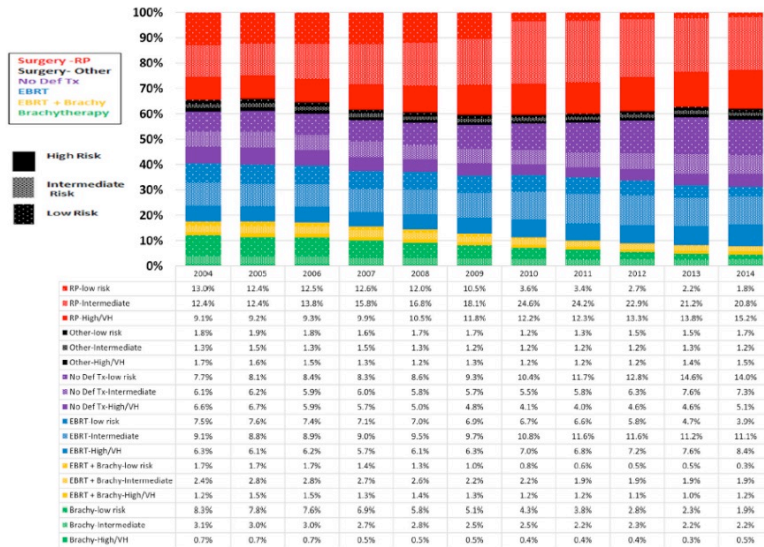


Factors influencing prostate cancer patterns of care: An analysis of treatment variation using the SEER database

Lindsay M. Burt MD, Dennis C. Shrieve MD, PhD,
 Jonathan D. Tward MD, PhD *

Is There Age Bias in the Treatment of Localized Prostate Carcinoma?

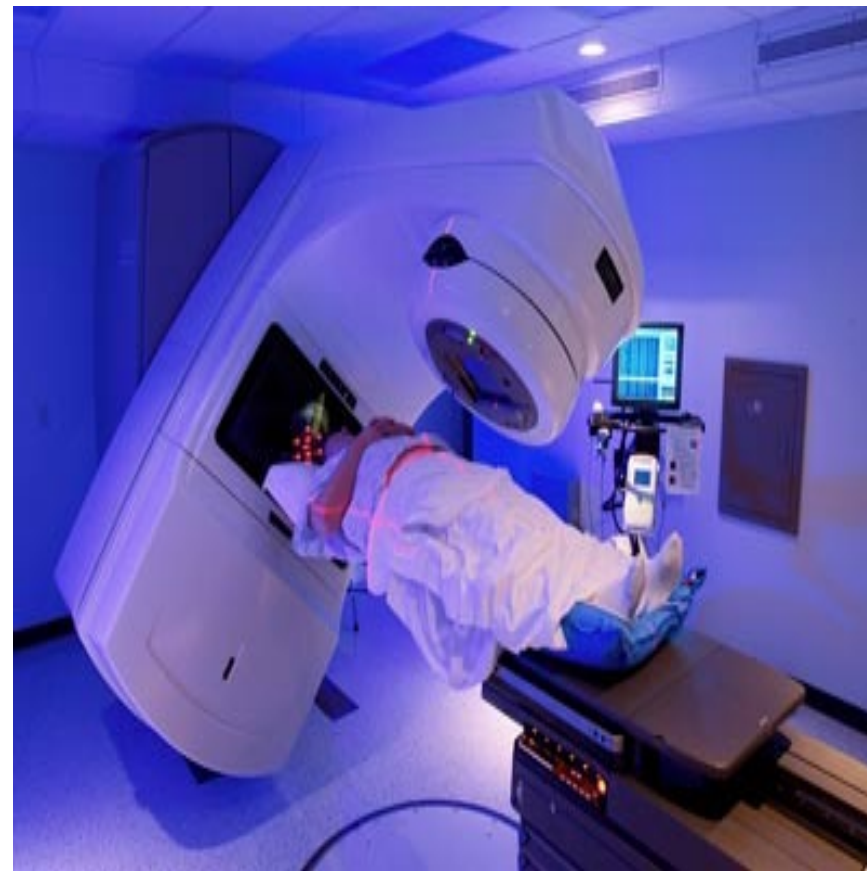
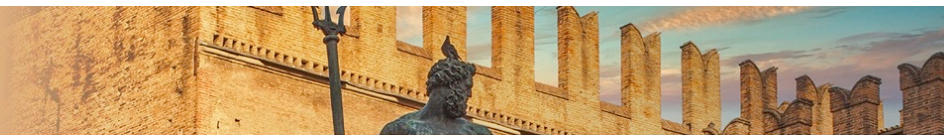
Time Trends of Localized Prostate Cancer by NCCN Risk Group



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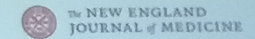


Radical Prostatectomy: The Good, The Bad and The Ugly



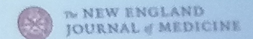
The role of radical prostatectomy in patients with localized disease – available RCTs

Radical Prostatectomy or Watchful Waiting in Early Prostate Cancer



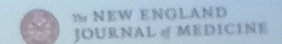
Bill-Axelsson et al. *N Engl J Med* 2018;379:2319-29

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



Hamdy et al. *N Engl J Med* 2016;375:1415-1424

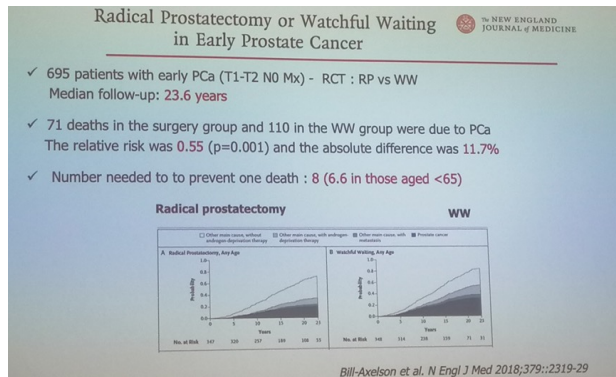
Follow-up of Prostatectomy versus Observation for Early Prostate Cancer



Wilt et al. *N Engl J Med* 2017;377,2



SPCG-4



Extended follow-up confirmed a substantial reduction in mortality after RP



The benefit of RP with respect to death from PC was largest in men younger than 65 (RR 0.50) and in those with intermediate-risk disease (RR 0.38)

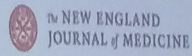
Table 2. End-Point Estimates at 23 Years and Relative Risk Over the 29-Year Trial Period.*

End Point	Radical Prostatectomy		Watchful Waiting		Absolute Difference in Risk at 23 Yr (95% CI)	No. Needed to Treat to Prevent End Point at 23 Yr (95% CI)	Relative Risk, Radical Prostatectomy vs. Watchful Waiting (95% CI)†	P Value‡
	No. of Events/ Total No.§	Cumulative Incidence at 23 Yr¶	No. of Events/ Total No.§	Cumulative Incidence at 23 Yr¶				
		%		%	percentage points			
Death from any cause								
All patients	261/347	71.9 (67.0–77.0)	292/348	83.8 (79.8–88.1)	12.0 (5.5–18.4)	8.4 (5.4–18.2)	0.74 (0.62–0.87)	<0.001
Patients <65 yr of age	105/157	62.6 (55.1–71.2)	129/166	77.6 (71.1–84.7)	15.0 (4.4–25.5)	6.7 (3.9–22.6)	0.62 (0.48–0.80)	—
Patients ≥65 yr of age	156/190	79.2 (73.4–85.4)	163/182	89.3 (84.6–94.3)	10.1 (2.4–17.8)	9.9 (5.6–41.4)	0.86 (0.69–1.07)	—
Death from prostate cancer								
All patients	71/347	19.6 (15.8–24.4)	110/348	31.3 (26.8–36.6)	11.7 (5.2–18.2)	8.6 (5.5–19.3)	0.55 (0.41–0.74)	<0.001
Patients <65 yr of age	39/157	22.8 (17.0–30.6)	63/166	37.9 (31.1–46.3)	15.1 (5.0–25.2)	6.6 (4.0–20.0)	0.50 (0.34–0.75)	—
Patients ≥65 yr of age	32/190	16.9 (12.3–23.1)	47/182	25.3 (19.7–32.6)	8.5 (0.2–16.8)	11.8 (6.0–601.0)	0.63 (0.40–0.99)	—
Distant metastasis**								
All patients	92/347	26.6 (22.3–31.7)	150/348	43.3 (38.3–48.9)	16.7 (9.6–23.7)	6.0 (4.2–10.4)	0.54 (0.42–0.70)	<0.001
Patients <65 yr of age	48/157	30.8 (24.3–39.0)	81/166	49.4 (42.2–57.8)	18.6 (7.9–29.2)	5.4 (3.4–12.7)	0.49 (0.34–0.70)	—
Patients ≥65 yr of age	44/190	23.2 (17.9–30.0)	69/182	37.7 (31.2–45.6)	14.6 (5.2–23.9)	6.9 (4.2–19.2)	0.59 (0.41–0.86)	—

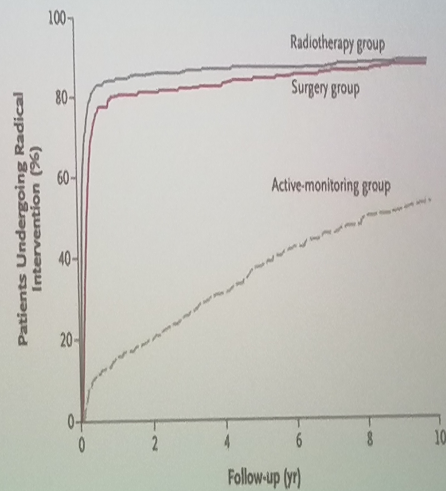
Bill-Axelson, NEJM, 2018



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



Cumulative probability of receiving an active treatment

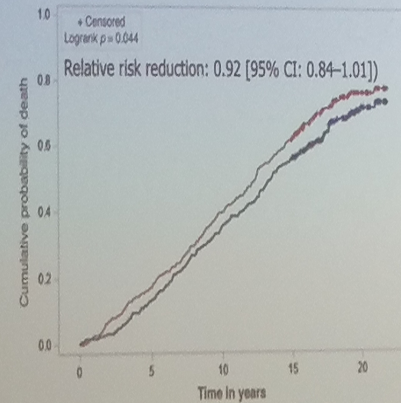


54.8% of the men assigned to active monitoring had received a radical treatment during follow-up

Hamdy et al. N Engl J Med 2016;375:1415-1424

Radical Prostatectomy or Observation for Clinically Localized Prostate Cancer: Extended Follow-up of the PIVOT Trial

✓ Median follow-up for survivors = 18.6 yr; inter-quartile range: 16.6-20.0

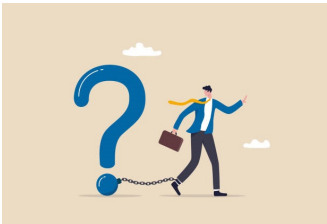


Number at risk

Group	0	5	10	15	20								
Observation	287	341	315	288	258	221	162	153	102	68	35	3	0
Radical prostatectomy	284	282	329	300	287	235	210	172	138	75	30	2	0

Subgroup	Radical prostatectomy events/n	Observation events/n	Hazard ratio (95% CI)	p value for interaction
Overall	246/284	289/287	0.92 (0.76, 1.09)	
Age				0.7
<65 yr	81/122	84/121	0.78 (0.55, 1.05)	
≥65 yr	179/242	185/228	0.98 (0.89, 1.06)	
Race				0.5
White	185/222	173/225	0.90 (0.84, 0.96)	
Black	74/111	87/121	0.99 (0.69, 1.32)	
Other	9/21	19/28	0.89 (0.38, 1.98)	
Charlson score				0.8
0	13/124	14/120	0.91 (0.64, 1.09)	
≥1	115/140	124/147	0.97 (0.87, 1.07)	
Performance score				0.7
0	203/212	223/210	0.93 (0.88, 1.00)	
1-4	43/52	46/57	0.80 (0.62, 1.01)	
PSA				0.3
≤10	167/228	160/241	0.86 (0.73, 1.02)	
>10	80/128	90/123	0.73 (0.53, 0.97)	
Local risk category				0.4
Low	80/148	90/143	0.93 (0.69, 1.24)	
Intermediate	89/129	97/123	0.89 (0.61, 0.93)	
High	60/77	62/80	0.83 (0.58, 1.18)	
Local Gleason score				0.2
≤7	159/254	180/261	0.77 (0.62, 0.95)	
7	53/69	49/64	0.82 (0.61, 1.10)	
≥8	25/35	19/32	0.87 (0.51, 1.50)	
ISUP risk scores				0.1
Low/II	279/311	321/313	0.89 (0.76, 1.03)	
Intermediate/III	118/177	108/167	0.74 (0.57, 0.96)	
High/IV-V	49/65	50/60	0.70 (0.47, 1.05)	
Percent cancer positive				0.1
≤25%	173/185	159/177	0.88 (0.75, 1.04)	
>25%	108/148	103/113	0.75 (0.58, 0.96)	

Wilt et al. Eur Urol, 2020; 77:713-24



Pending questions for the Surgeon

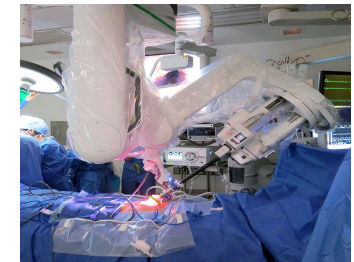
JAMA Network | **Open**



Invited Commentary | Urology

Robotic, Laparoscopic, and Open Radical Prostatectomy—Is the Jury Still Out?

Jeffrey M. Howard, MD, PhD

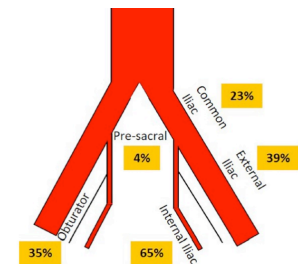


Platinum Priority – Prostate Cancer – Editor's Choice
 Editorial by Axel Heidenreich on pp. 605–606 of this issue.



Extended Versus Limited Pelvic Lymph Node Dissection During Radical Prostatectomy for Intermediate- and High-risk Prostate Cancer: Early Oncological Outcomes from a Randomized Phase 3 Trial

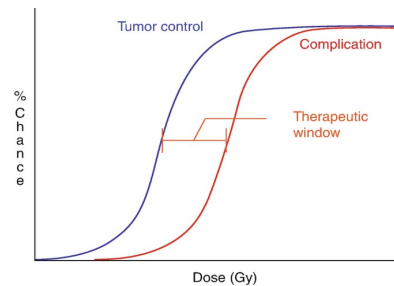
Jean F.P. Lestingi^{a,*}, Giuliano B. Guglielmetti^a, Quoc-Dien Trinh^b, Rafael F. Coelho^a,
 Jose Pontes Jr.^a, Diogo A. Bastos^a, Mauricio D. Cordeiro^a, Alvaro S. Sarkis^a, Sheila F. Faraj^a,
 Anuar I. Mitre^a, Miguel Srougi^a, William C. Nahas^a





Radiotherapy in localized PCa: The Dose Escalation Saga

Study	N	Design	Results on PSA control
Pollack 2002 ⁵ Kuban 2008 ⁶ M.D. Anderson Zietman 2005 ⁷	301	70 vs 78 Gy	bDFS in high-dose group significantly better (78% vs 59%); largest benefit in patients with PSA > 10 ng/mL
MGH/Loma Linda Peeters 2006 ⁸ Al-Mamgani 2008 ⁹ Dutch trial	393	70.2 vs 79.2 Gy	5-year bDFS significantly better in high-dose group (91.3% vs 78.8%)
Deamaley 2007 ¹⁰ MRC RT01	669	68 vs 78 Gy (±LHRH)	7-year bDFS significantly better in high-dose group (56% vs 45%)
	843	64 vs 74 Gy (±LHRH)	5-year bDFS significantly better in high-dose group (71% vs 60%)





CLINICAL INVESTIGATION

Prostate

Prostate Cancer Dose Escalation 1.0

HIGHER-THAN-CONVENTIONAL RADIATION DOSES IN LOCALIZED PROSTATE CANCER TREATMENT: A META-ANALYSIS OF RANDOMIZED, CONTROLLED TRIALS

GUSTAVO ARRUDA VIANI, M.D., EDUARDO JOSE STEFANO, M.D., AND SERGIO LUIS AFONSO, M.D.

Department of Radiation Oncology, Marília School of Medicine, São Paulo, Brazil



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

JAMA Oncol. 2018;4(6):e180039. doi:10.1001/jamaoncol.2018.0039

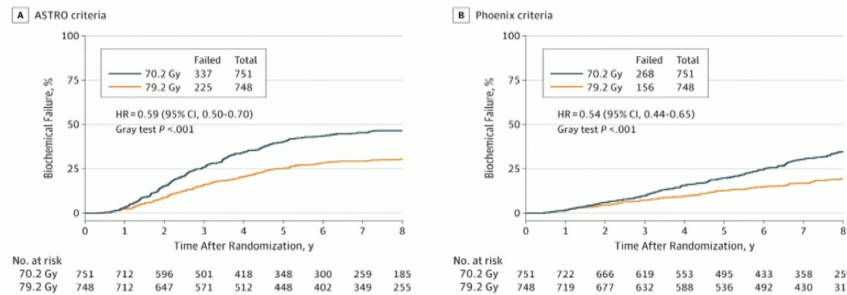
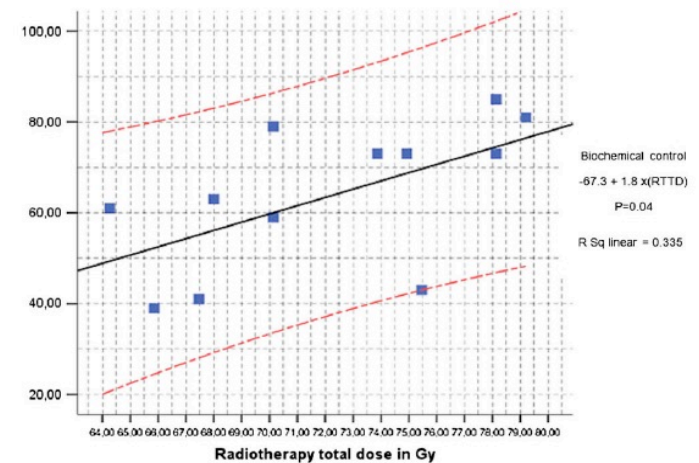
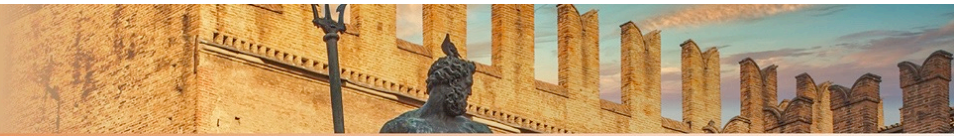


Figure Legend:
Biochemical Failure (American Society for Therapeutic Radiology and Oncology [ASTRO] Consensus Definition and Phoenix Criteria) After Either Conventional-Dose (70.2 Gy) or High-Dose (79.2 Gy) Radiation Therapy HR indicates hazard ratio.



Increasing Total Dose reduces the risk of BR by approximately 1.8% for each 1-Gy increase

Between 70 and 80 Gy, a significant increase in the 5-year BC rate (14%, 17.8% and 19.2% in low, intermediate and high-risk patients)



LATE RECTAL TOXICITY: I RADIOTHERAPY

EUGENE H. HUANG, M.D.,* AI
 GEORGE STARKSCHALL, PH.D.,
 DEBC

Departments of *Radiation Oncology, †Biomathemati
 Center, Houston, Texas; †Department of

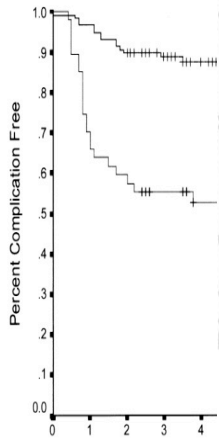
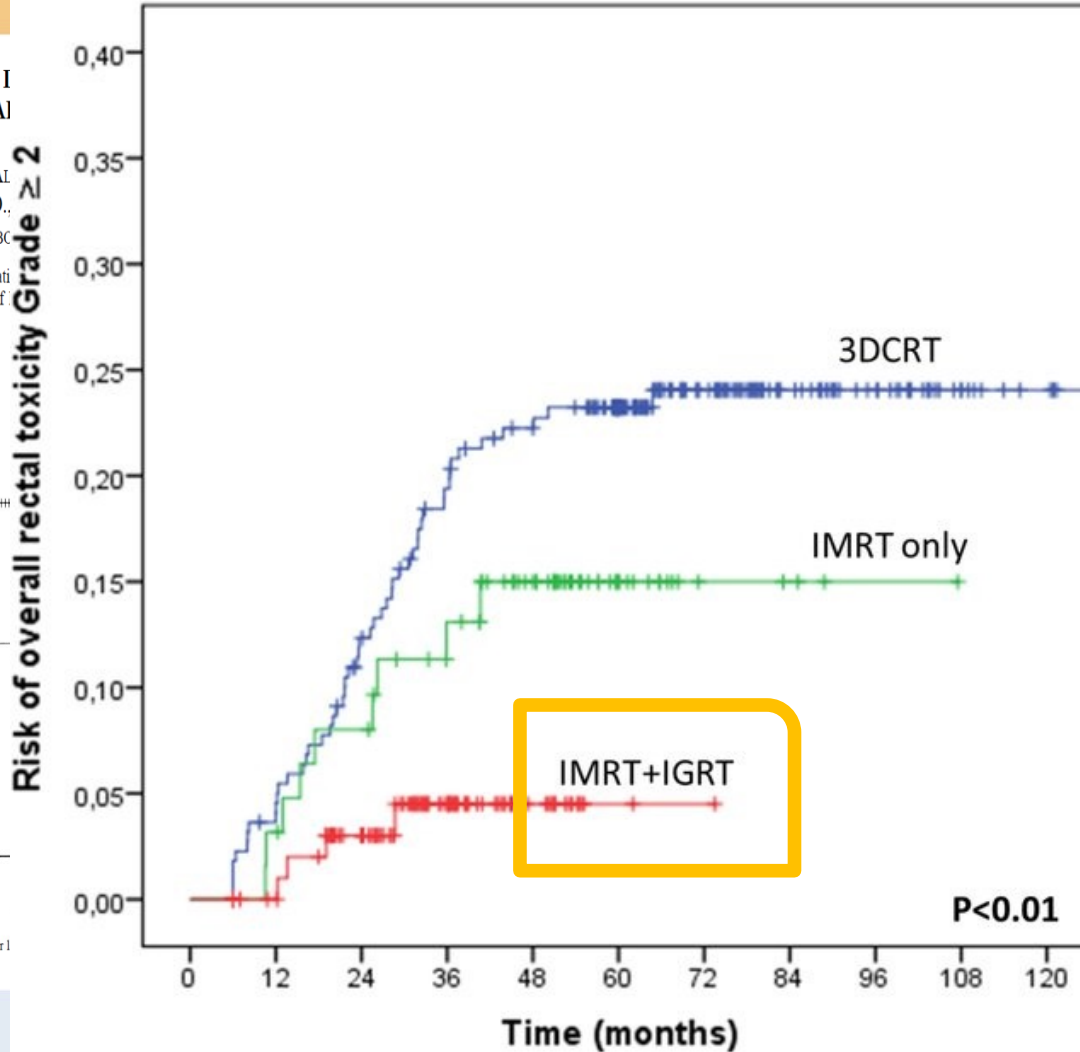
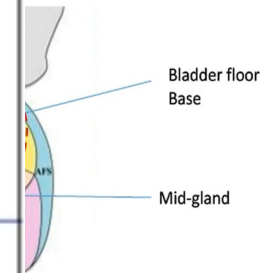


Fig. 2. Kaplan-Meier freedom from Grade 2 or higher l
 volume receiving ≥ 70 Gy.



WITH HIGH DOSE RT- **Avoid TOXICITY**



CAVE:

1. Urethra delineation e.g. in T2WI (better with catheter for EBRT phase ?)
2. Dose limit Urethra: no hot spots
3. Use rectal spacers !

long-term cystitis with high dose in base urethra
 ce in the mid-gland urethra

Review of Evidence / **Lessons learned**

on is required in ALL risk strata

ence

n to EQD2 of about 80 Gy is required

ence

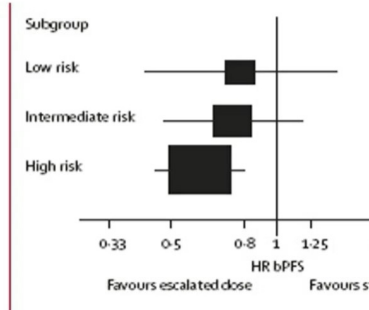


Novel insights...

ANALYSIS OF INTRAPROSTATIC FAILURES IN PATIENTS TREATED WITH HORMONAL THERAPY AND RADIOTHERAPY: IMPLICATIONS FOR CONFORMAL THERAPY PLANNING

NUMA CELLINI, M.D., ALESSIO G. MORGANTI, M.D., GIAN C. MATTIUCI, M.D.,
 VINCENZO VALENTINI, M.D., MARIAVITTORIA LEONE, M.D., STEFANO LUZI, M.D.,
 M.D., NICOLA DINAPOLI, M.D., CINZIA DIGESU', M.D., AND DANIELA SMANIOTTO, M.D.

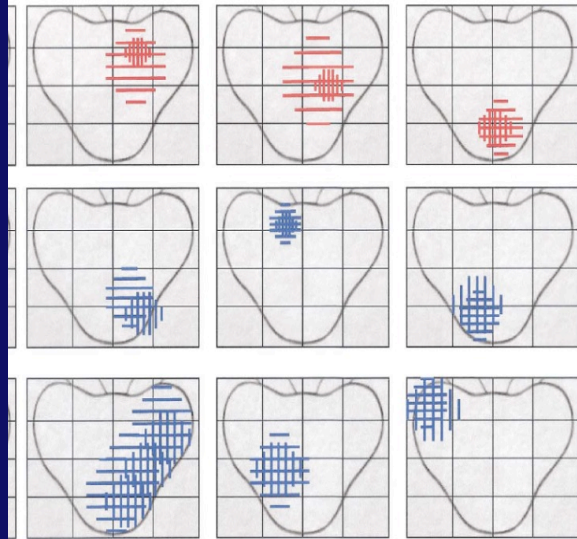
Which Risk Groups do benefit from



Deernalay et al, Lancet Oncol, 2007

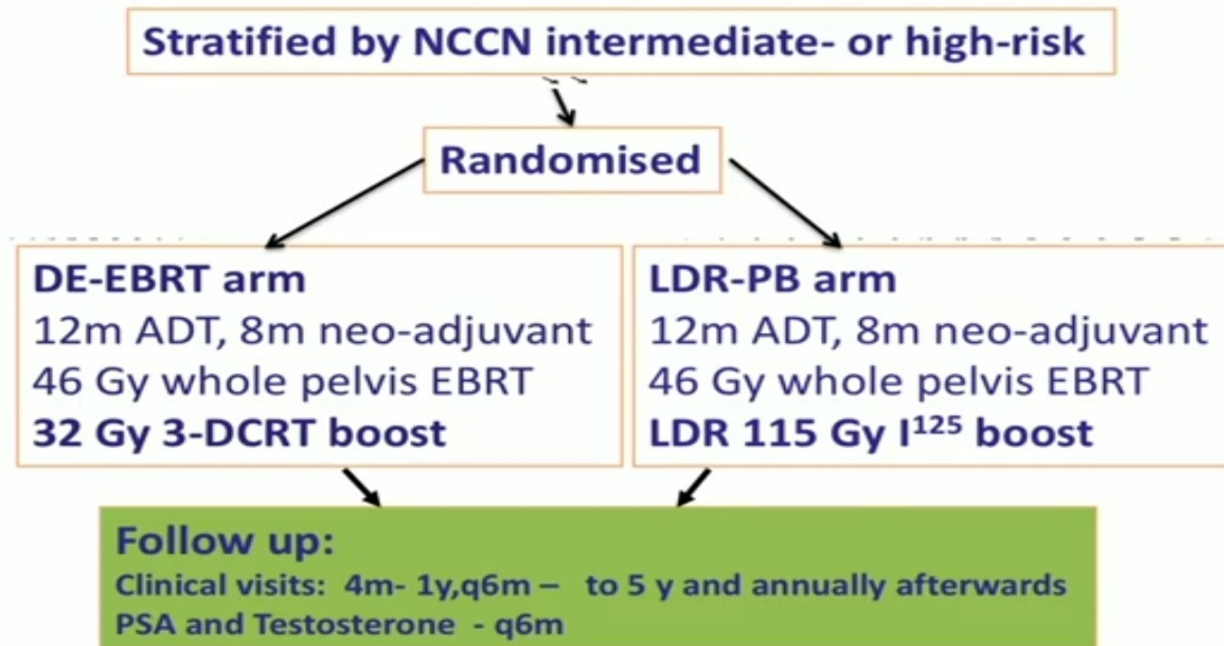
Recurrence of Cancer After RT in the Dominant Pre-Treatment Lesion (Pucar et al MSKCC IJROBP 2007)

A				pT2c; tumors: 0.73 cm ³ (right), < 0.01 cm ³ (left)
B				pT2c; tumor: 0.22 cm ³
C				pT3a; tumor: 1 cm ³

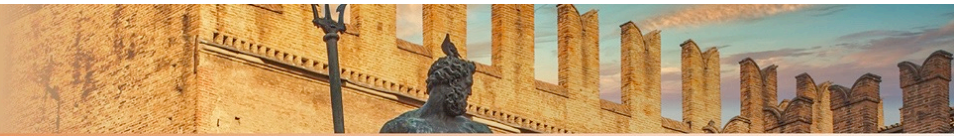




ASCENDE-RT simplified schema



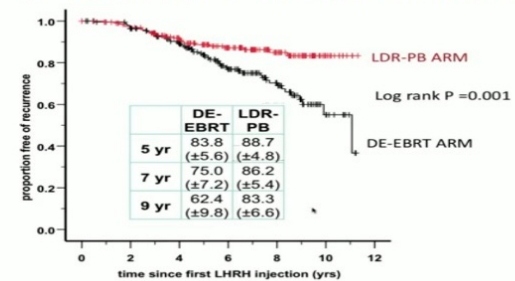
Morris et al IJROBP 2017



ASCENDE RT trial: meaningful results

Results: Biochemical PFS

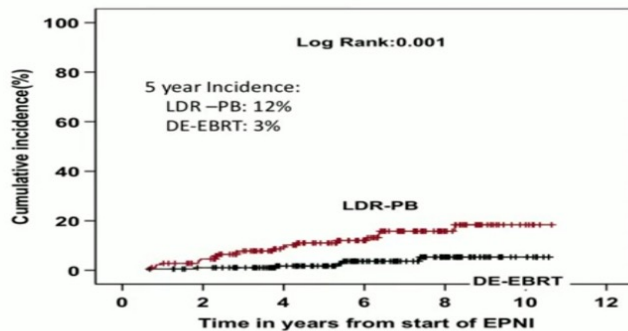
Intent-to-treat analysis of the primary endpoint



Morris et al IJROBP 2017

EBRT+ADT vs EBRT+brachy+/- ADT

Cumulative incidence Late catheterization

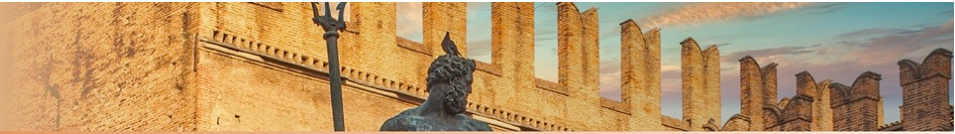


Rodda et al IJROBP 2017

Table 1. Overview of Outcomes From the Three Randomized Combination Brachytherapy Trials

Trial	No.	Media Follow-up (years)	BCR* (%)	Oncologic Outcomes			Late GU Toxicity		Late GI Toxicity	
				DM	CSS	OS	Absolute Rates (%)	Relative G ≥ 3 Increase from Brachytherapy	Absolute Rates (%)	Relative G ≥ 3 Increase from Brachytherapy
ASCENDE-RT	398	6.5	7 years: 86 v 75	P = .83†	P = .32†	P = .29†	G2: 32.8 v 20.6 G3: 18.4 v 5.2 G4 or 5: 1.0 v 0	3.7-fold higher	G2: 31.3 v 20.2 G3: 8.1 v 3.2 G4 or 5: 2.1 v 0.6	2.7-fold higher
Sathya ¹⁷	104	14.0	14 years: 53 v 30	P = .32†	P = .83†	P = .99†	G ≥ 3: 13.7 v 3.8	3.6-fold higher	G ≥ 3: 3.9 v 1.9	2-fold higher
Summary	720		Significant decrease in BCR	NS difference in DM	NS difference in CSS	NS difference in OS	Structures: 8 v 2 Significant absolute increase of approximately 10% in severe late GU toxicity	4-fold higher Approximately 3- to 4-fold increased severe late GU toxicity	Significant absolute increase of approximately 5% in severe late GI toxicity	Approximately 2-fold increased severe late GI toxicity

Spratt, JCO, 2017



Dose Escalation 2.0 : The Firestarter



original reports

Focal Boost to the Intraprostatic Tumor in External Beam Radiotherapy for Patients With Localized Prostate Cancer: Results From the FLAME Randomized Phase III Trial

Linda G. W. Kerkmeijer, MD, PhD^{1,2}; Veerle H. Groen, MD¹; Floris J. Pos, MD, PhD³; Karin Haustermans, MD, PhD⁴; Evelyn M. Monnikhof, PhD³; Robert Jan Smeenk, MD, PhD²; Martina Kunze-Busch, PhD²; Johannes C. J. de Boer, PhD¹; Jochem van der Voort van Zijp, MD, PhD¹; Marco van Vulpen, MD, PhD⁶; Cédric Draulans, MD, PhD⁴; Laura van den Bergh, MD, Sofie Isebaert, PhD⁴; and Uulke A. van der Heide, PhD³

FLAME Study

Randomized Comparison Whole Gland Conventionally Fractionated Radiotherapy (CFR) to CFR with an Integrated Boost up to 95 Gy

- Phase III multi-center randomized trial in 3 centers in the Netherlands
- Intermediate and high risk eligible
- Control Arm: Prostate treated to 77 Gy in 35 fx of 2.2 Gy to entire prostate
- Experimental Arm: Additional integrated boost to the DIL of 95 Gy in 35 fx of 2.7 Gy
- DIL defined on mp-MRI



Inclusion:

- Intermediate- and high-risk prostate cancer

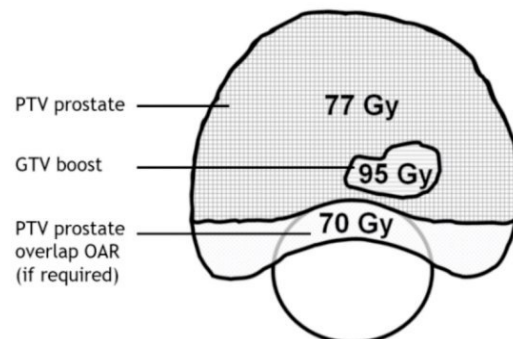
Exclusion:

- TURP <3 months
- IPSS >20
- N+M+
- Pelvic RT or prostatectomy
- MRI contra-indications

- PTV 77Gy in 35 fractions (EQD2 82Gy*)
- +/- focal boost up to 95Gy (EQD2 116Gy*)
- One or more GTV's contoured on mp-MRI
- OAR constraints >>> boost dose

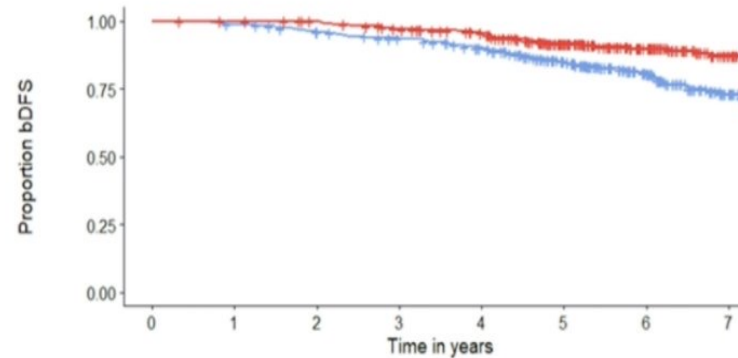


FLAME approach



FLAME primary endpoint

Biochemical disease free survival



ESTRO2020

FLAME focal boost arm
 Standard arm

Intention to treat:

- Kaplan Meier: log-rank $p < 0.001$
- 5-year bDFS: 85% vs 92% (95%CI 4-10% difference)



	Genitourinary toxicity				Gastrointestinal toxicity			
	77Gy	95Gy	Difference % (95% CI)	p-value	77Gy	95Gy	Difference % (95% CI)	p-value
Grade ≥ 2	23.0	27.8	4.8 (-2.3 - 12.0)	0.19	12.2	12.7	0.5 (-5.0 - 5.9)	0.86
Grade ≥ 3	3.5	5.6	2.1 (-1.3 - 5.6)	0.22	1.4	1.4	0 (-1.9 - 2.0)	0.99



Phase III randomised trial

Standard whole prostate gland radiotherapy with and without lesion boost in prostate cancer: Toxicity in the FLAME randomized controlled trial



Evelyn M. Monninkhof^{a,b}, Juliette W.L. van Loon^b, Marco van Vulpen^b, Linda G.W. Kerkmeijer^b, Floris J. Pos^c, Karin Haustermans^d, Laura van den Bergh^d, Sofie Isebaert^d, Gill M. McColl^e, Robert Jan Smeenk^e, Juus Noteboom^b, Iris Walraven^c, Petra H.M. Peeters^a, Uulke A. van der Heide^{c,*}

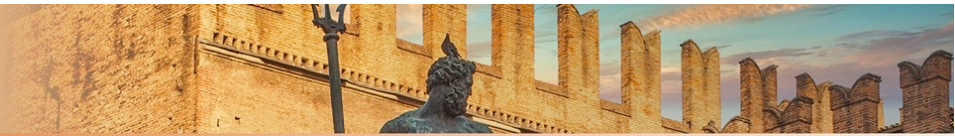
Original Article

Anorectal dose-effect relations for late gastrointestinal toxicity following external beam radiotherapy for prostate cancer in the FLAME trial



Veerle H. Groen^a, Nicolaas P.A. Zuithoff^b, Marcel van Schie^c, Evelyn M. Monninkhof^b, Martina Kunze-Busch^d, Hans C.J. de Boer^a, Jochem van der Voort van Zyp^a, Floris J. Pos^c, Robert Jan Smeenk^d, Karin Haustermans^e, Sofie Isebaert^e, Cédric Draulans^e, Tom Depuydt^e, Helena M. Verkooijen^f, Uulke A. van der Heide^c, Linda G.W. Kerkmeijer^{a,d,*}

^aUniversity Medical Center Utrecht, Radiation Oncology; ^bJulius Center for Health Sciences and Primary Care, University Medical Center, Utrecht University; ^cThe Netherlands Cancer Institute, Radiation Oncology, Amsterdam; ^dRadboud University Medical Centre, Radiation Oncology, Nijmegen, The Netherlands; ^eUniversity Hospitals Leuven, Radiation Oncology, Belgium; ^fUniversity Medical Center, Imaging Division, Utrecht, The Netherlands



Prostate Cancer Radiotherapy: The Room is On Fire

Standard treatment	FLAME (NCT01168479; phase III)	hypo-FLAME (NCT02853110; phase II)	hypo-FLAME 2.0 (NCT04045717; phase II)
OTT = 7-8 weeks	OTT = 7 weeks	OTT = 29 days	OTT = 15 days
35-40 fractions, 5x/week	35 fractions, 5x/week	5 fractions, 1x/week	5 fractions, 2x/week
Whole gland irradiation	Whole gland irradiation ± focal tumour boost	Whole gland irradiation + focal tumour boost	Whole gland irradiation + focal tumour boost
<p>Prostate</p> <p>Tumour</p>	<p>Prostate</p> <p>Tumour</p>	<p>Prostate</p> <p>Tumour</p>	<p>Prostate</p> <p>Tumour</p>



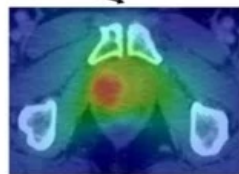
Study Protocol

PSMA-PET/MRI-Based Focal Dose Escalation in Patients with Primary Prostate Cancer Treated with Stereotactic Body Radiation Therapy (HypoFocal-SBRT): Study Protocol of a Randomized, Multicentric Phase III Trial

Constantinos Zamboglou ^{1,2,3,4,†}, Simon K. B. Spohn ^{1,2,3,*,†}, Sonja Adebahr ^{1,2,†}, Maria Huber ⁵, Simon Kirste ^{1,2}, Tanja Sprave ^{1,2}, Christian Gratzke ⁶, Ronald C. Chen ⁷, Ernst Günther Carl ⁸, Wolfgang A. Weber ⁹, Michael Mix ¹⁰, Matthias Benndorf ¹¹, Thomas Wiegel ¹², Dimos Baltas ¹³, Carolin Jenkner ⁵ and Anca L. Grosu ^{1,2}

HypoFocal-SBRT

374 patients
Unfavorable Intermediate- / High-Risk PCa
Staged cN0 and cM0 in PSMA-PET/CT and MRI



Control Arm

MHRT
Prostate + SV
46.4 Gy in 20 Fractions
Prostate:
60-62 Gy in 20 Fractions

Experimental Arm

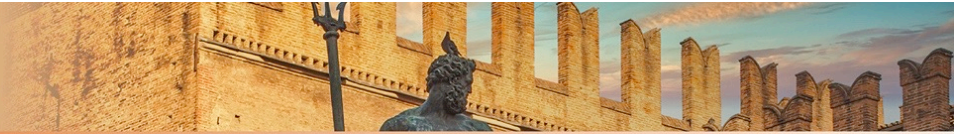
SBRT
Prostate + SV:
30 Gy in 5 Fractions
Prostate:
35 Gy in 5 Fractions
Focal Boost Based on PSMA-PET/MRI:
40-42 Gy in 5 Fractions



Focal Dose Intensification to the Dominant Intraprostatic Lesion (DIL) Using an MR-Linac Adaptive-Planning Approach for Prostate Cancer: Dosimetric Outcomes and Early Toxicity

V.S. Brennan,¹ S. Bureson,² C. Kostrzewa,³ P. G. Scribes,² E. Subashi,² Z. Zhang,³ N. Tyagi,² and M.J. Zelefsky¹; ¹Department of Radiation Oncology, Memorial Sloan Kettering Cancer Center, New York, NY, ²Department of Medical Physics, Memorial Sloan Kettering Cancer Center, New York, NY, ³Department of Epidemiology and Biostatistics, Memorial Sloan Kettering Cancer Center, New York, NY





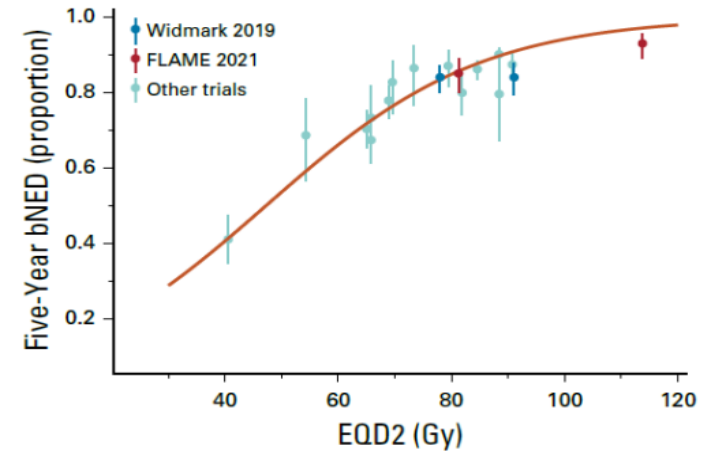
correspondence

Radiation Dose Escalation for Early Prostate Cancer: Reigniting the FLAME?

TO THE EDITOR:

Kerkmeijer et al,¹ the investigators of the FLAME randomized controlled trial of radiation dose-painting for early prostate cancer, are to be congratulated for a trial that tests a new concept for how to intensify therapy

Vogelius I, Bentzen S, JCO Correspondence 2021



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EDITORIAL | VOLUME 113, ISSUE 2, P302-304, JUNE 01, 2022

Are We Ready for Focal Dose Radio-Ablation in the Treatment of Localized Prostate Cancer?

Michael J. Zelefsky, MD 👤 ✉



Does dose escalated radiation allow ADT "discounting"?

RTOG 0815: Phase III Trial of Dose Escalated RT +/- ADT

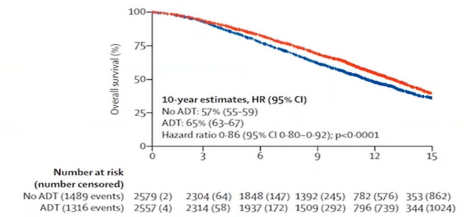
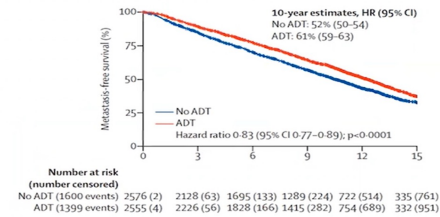


Androgen deprivation therapy use and duration with definitive radiotherapy for localised prostate cancer: an individual patient data meta-analysis

Amar U Khan*, Yikun Sun*, Holly Hartman, Thomas M Pisansky, Michel Bolla, Anouk Neven, Allison Steigler, James W Denham, Felix Y Feng, Almudena Zapatero, John G Armstrong, Abdenour Nabid, Nathalie Carrier, Luis Souhami, Mary T Dunne, Jason A Ejstathiou, Howard M Sandile, Araceli Guerrero, David Joseph, Philippe Maingon, Theo M de Rooij, Xavier Makinodan, Ting Martin Ma, Tahmineh Romero, Xiaoyan Wang, Matthew B Rettig, Robert E Reiter, Nicholas G Zaorsky, Michael L Steinberg, Nicholas G Nickols, Angela Y Jia, Jorge A Garcia, Daniel E Spratt, the MARCAP Consortium group?

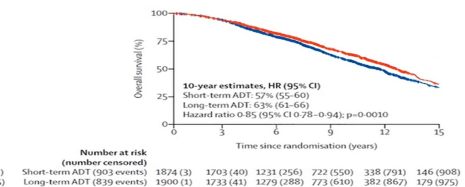
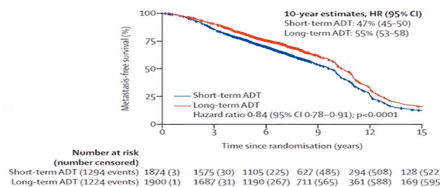


- 12 randomised Phase-III-Trials
- N=10.853 pts.
- 1962-2020
- Median FU: 11.4 years (RT vs. RT + ADT)
- 1. ADT use (3-4 mo. - 6-9 mo.)
- 2. Neoadjuvant extension (4-6 mo. - 18-36 mo.)
- 3. Adjuvant prolongation
- Unplanned Analysis



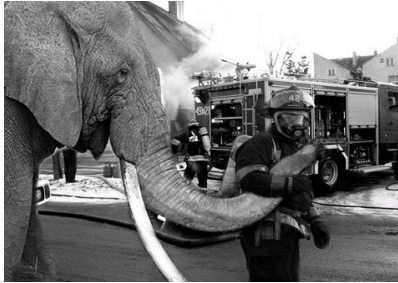
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PROSTATE CANCER | VOLUME 82, ISSUE 1, P106-114, JULY 01, 2022

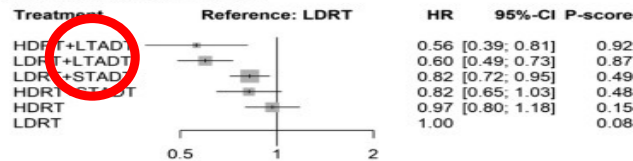
High-dose Radiotherapy or Androgen Deprivation Therapy (HEAT) as Treatment Intensification for Localized Prostate Cancer: An Individual Patient-data Network Meta-analysis from the MARCAP Consortium

Amar U. Kishan • Xiaoyan Wang • Yilun Sun • ... Jorge A. Garcia • Daniel E. Spratt •

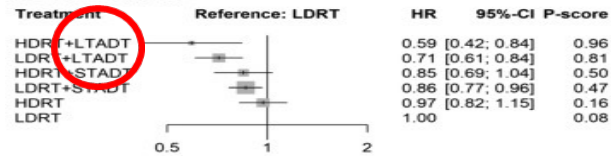
MARCAP Consortium [†] • [Show all authors](#) • [Show footnotes](#)

Published: April 22, 2022 • DOI: <https://doi.org/10.1016/j.eururo.2022.04.003> • Check for updates

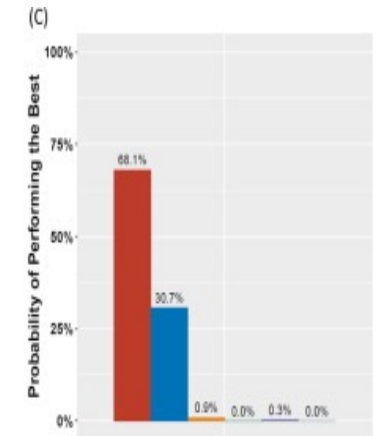
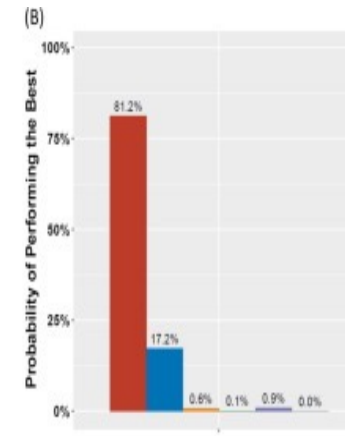
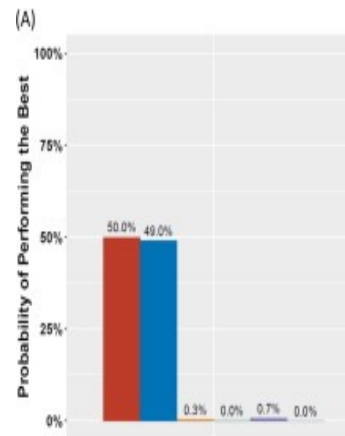
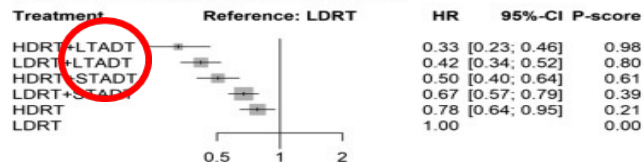
A. Metastasis-free survival

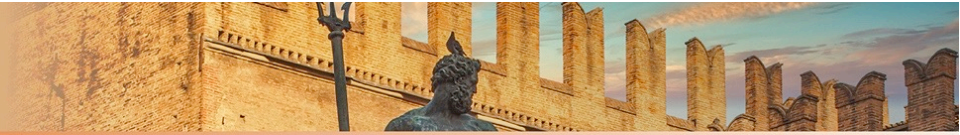


B. Overall survival



C. Biochemical recurrence-free survival





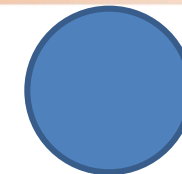
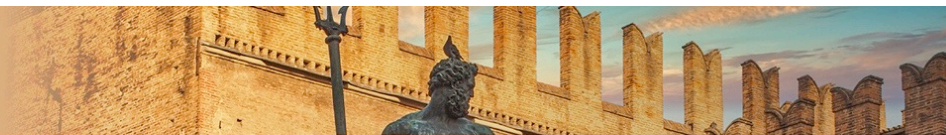
Take-home messages

- The influence of age at diagnosis on PC outcomes remains unclear; at least a subgroup of younger pts may have an overall poorer prognosis than older pts
- A more intensified and multimodal curative approach may be offered to these patients, especially those with lower competing mortality risk
- Modern IGRT and online adaptive treatment improve the capacity to boost the tumor by EBRT without increasing the dose to the surrounding organs at risk
- ADT should be routinely offered along with RT in intermediate and high-risk prostate cancer patients, irrespective of radiotherapy dose
- Treatment intensification should always take patients QoL into account

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Radioterapia di precisione per un'oncologia innovativa e sostenibile



Thank You For Your Attention