Intermediate-Risk Organ-Confined Prostate Cancer: Do We Know What's Best?

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Disclosures for Christian Kratzik, LLD, MD

none

Disclosures for Felix Sedlmayer, MD

none

Intermediate-Risk Prostate Cancer

At least one of the following:

- PSA level is between 10 and 20 ng/mL
- Gleason score is 7
- T stage is T2b or T2c

Pretreatment Risk of Recurrence

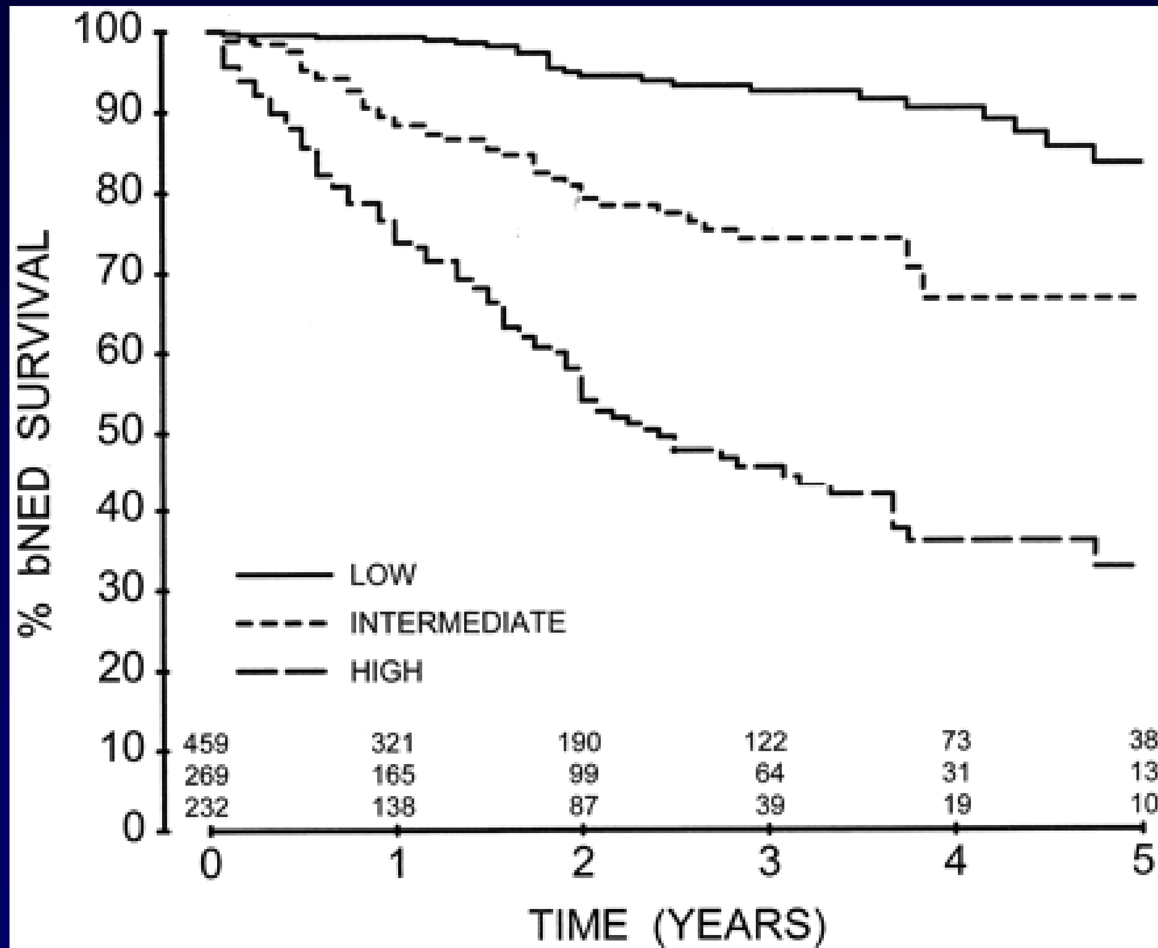
63-year-old patient (medical oncologist)
PSA:11 ng/mL
T2b -Tumor
5 of 12 cores positive (all on one side)
Gleason score 7 (4+3)

D‘Amico Risk Stratification for Prostate Cancer

	PSA ng/mL	Gleason sum	Clinical stage
Low risk	≤ 10	≤ 6	≤T2a
Intermediate risk	10-20	7	T2b
High risk	≥ 20	8-10	≥T2c

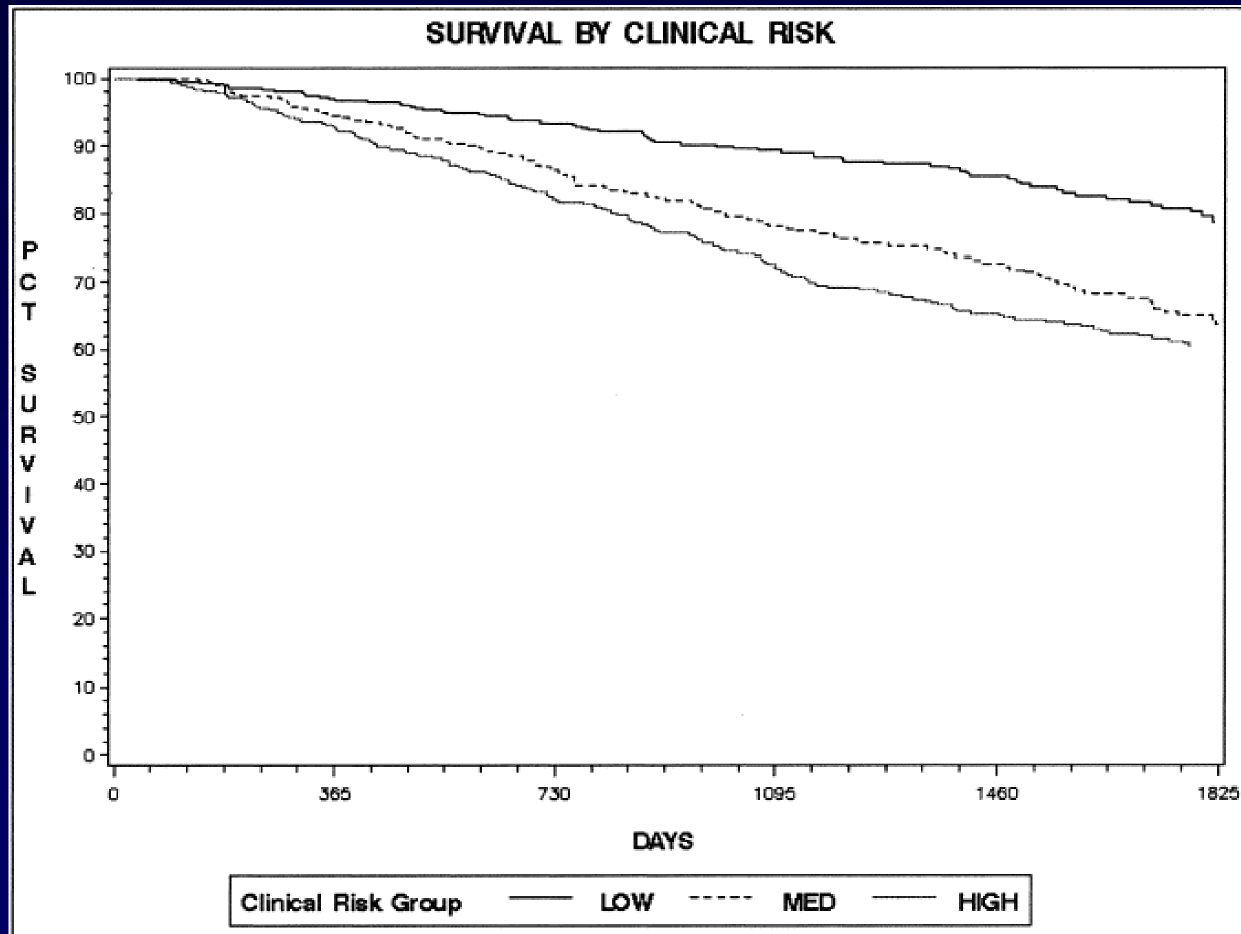
D’Amico AV, et al. *J Clin Oncol.* 2000;18(6):1164-1172.

PSA Failure-Free Survival Using the PSA Value, Biopsy, Gleason Score, and Clinical T Stage



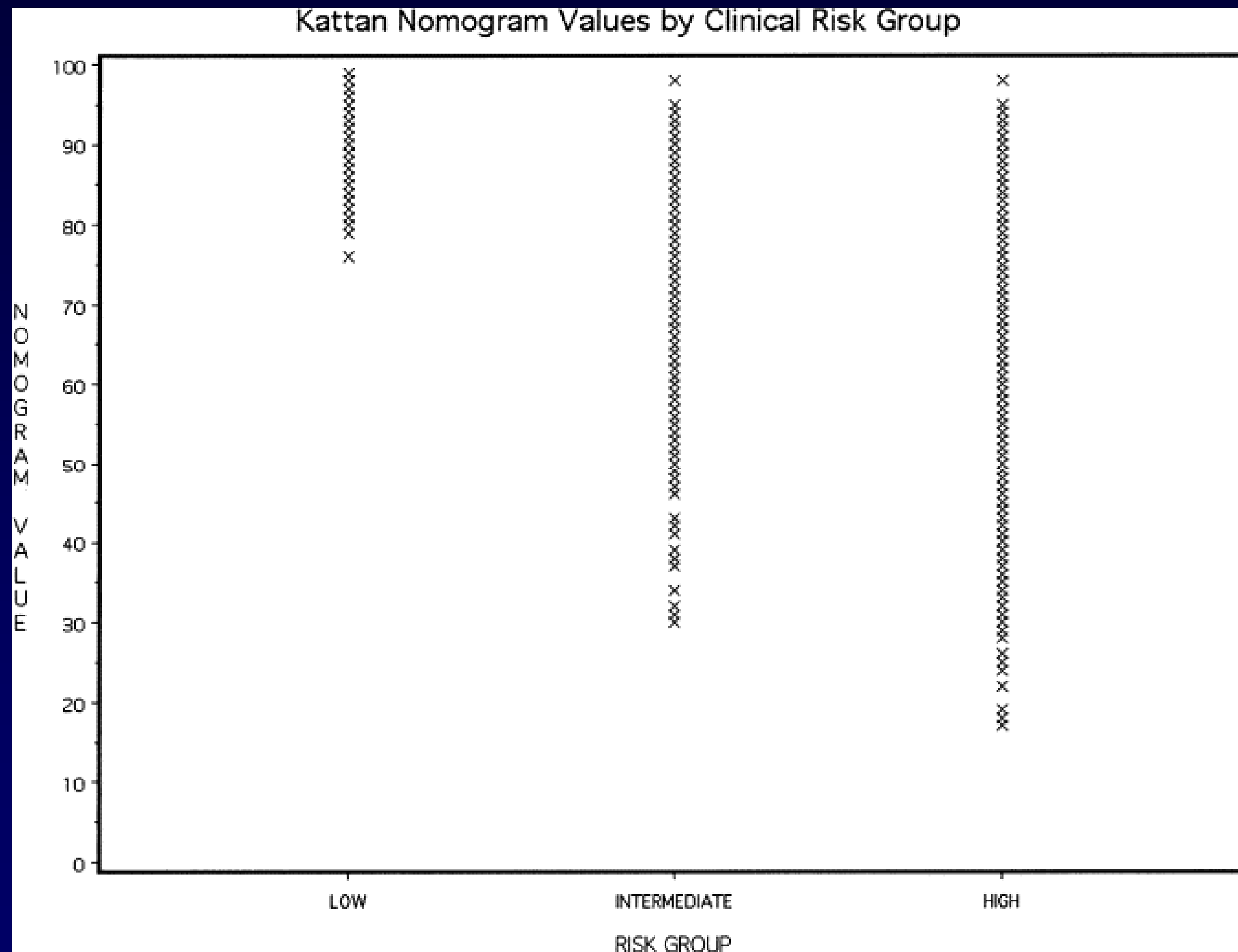
D'Amico AV, et al. *J Clin Oncol.* 2000;18(6):1164-1172.

Actuarial Kaplan-Meier CaPSURE Recurrence-Free Survival Curves for D'Amico Risk Groups



Mitchell JA, et al. *J Urol.* 2005;173(4):1126-1131.

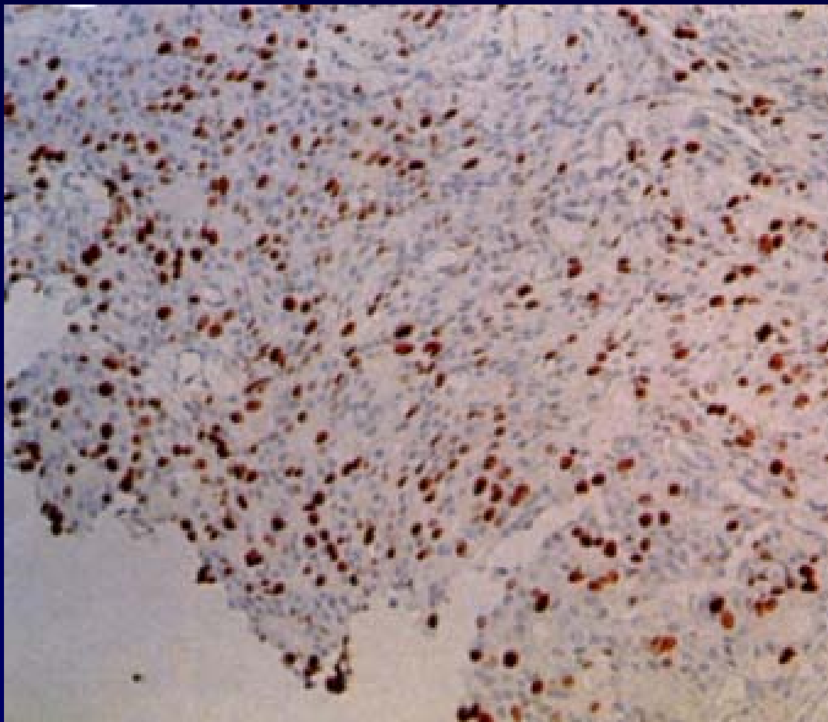
Kattan Nomogram Predicted 5-Year Recurrence-Free Survival for D'Amico Risk Groups



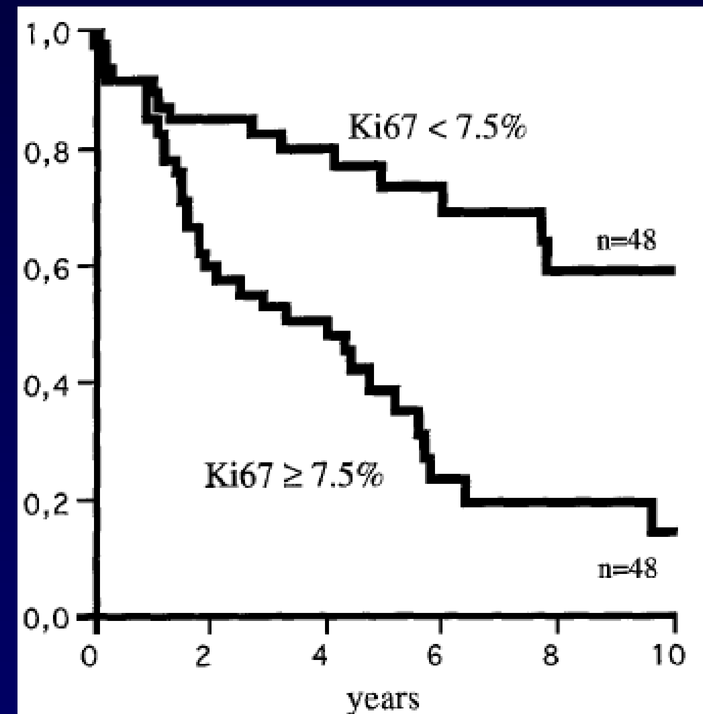
Mitchell JA, et al. *J Urol.* 2005;173(4):1126-1131.

Ki-67 Labeling Index in Core Needle Biopsies

Pos Ki67 staining in 30% of tumor cell nuclei

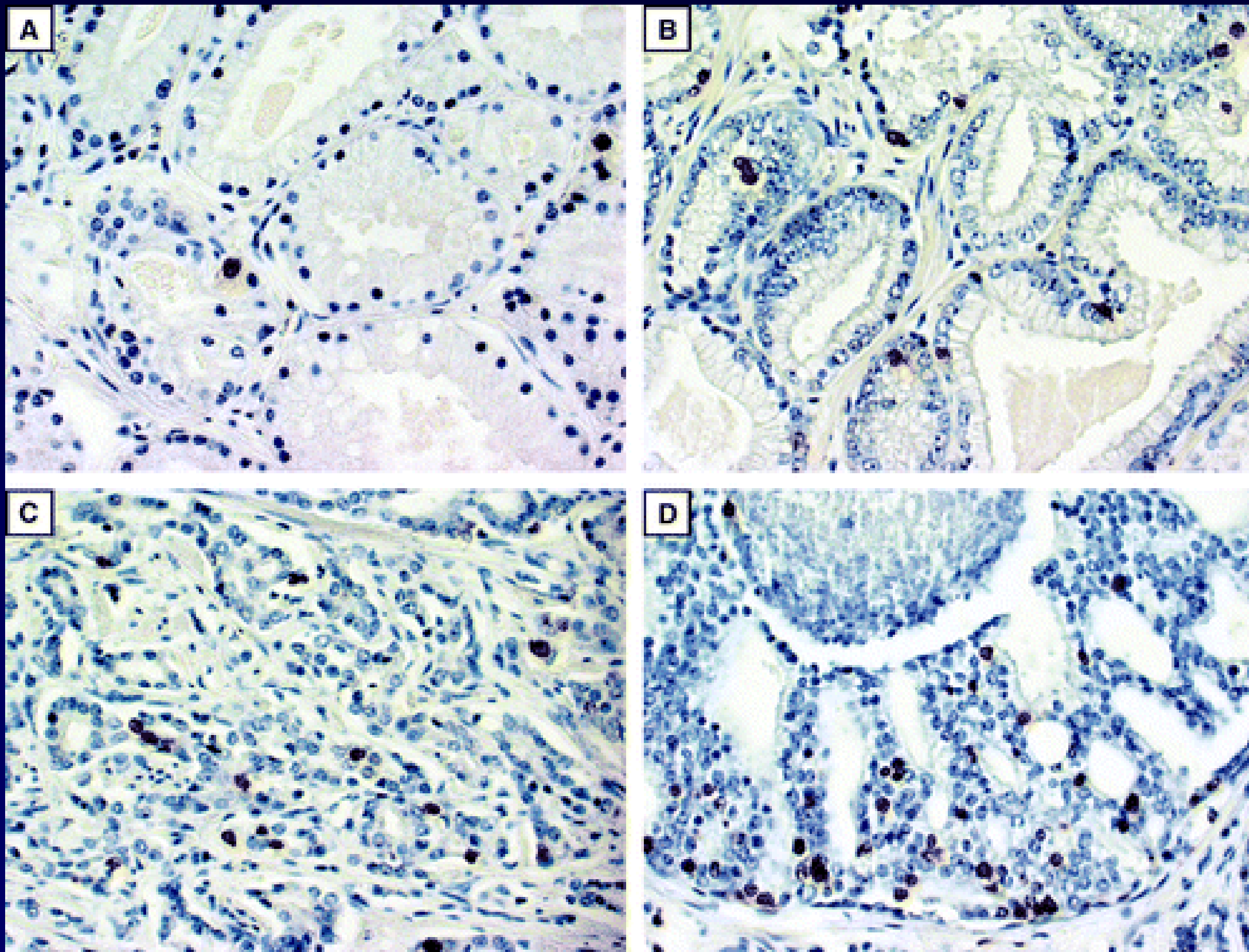


Ki67 Labeling Index and tumor-specific survival



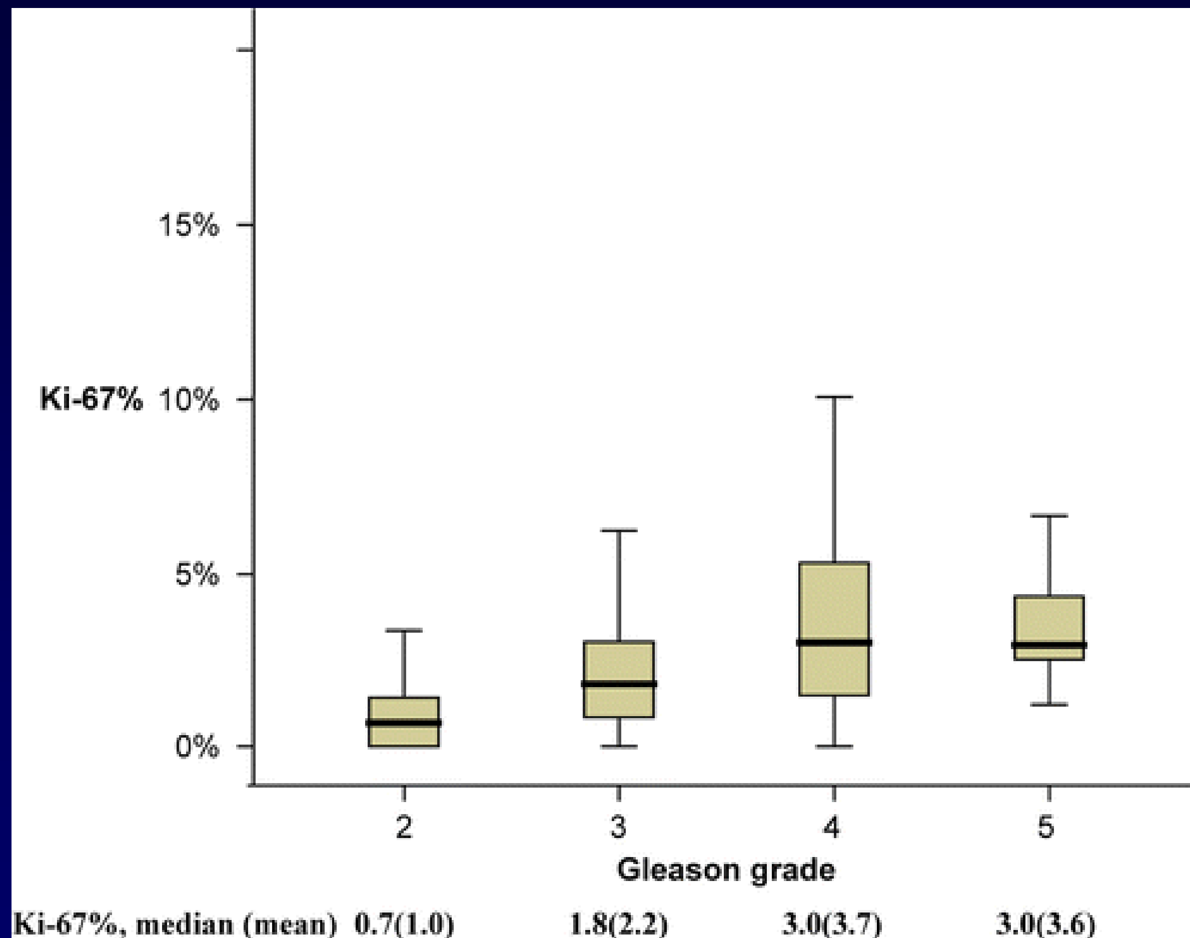
Bubendorf L, et al. *Hum Pathol.* 1998;29(9):949-954.

Ki-67 Nuclear Immunostaining in Various Gleason Grade PCa



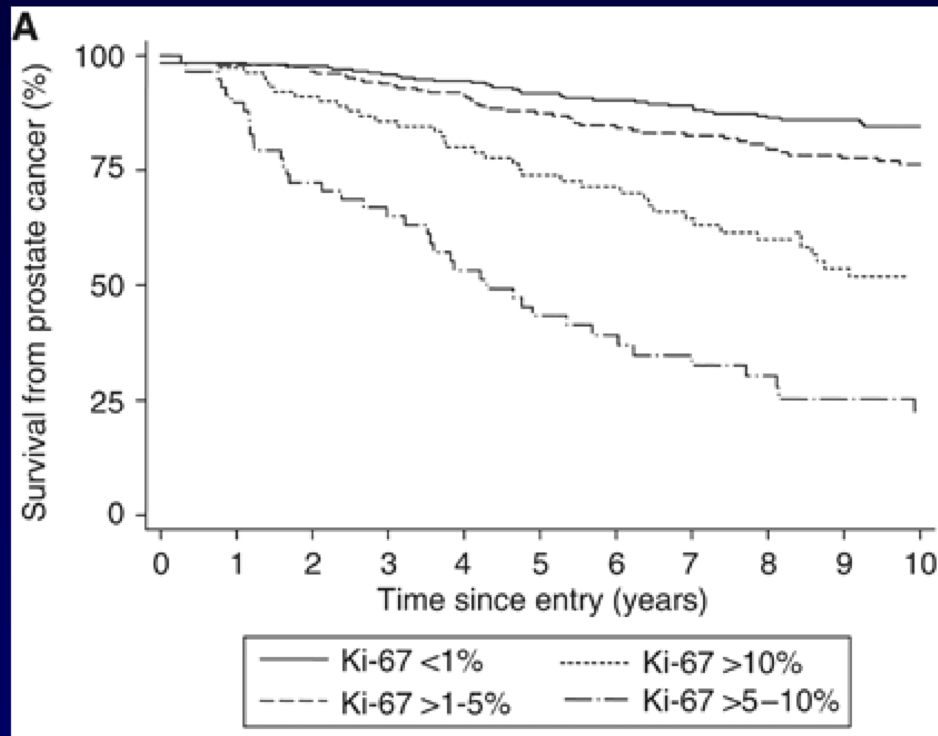
Khatami A, et al. *Scand J Urol Nephrol.* 2009;43(1):12-18.

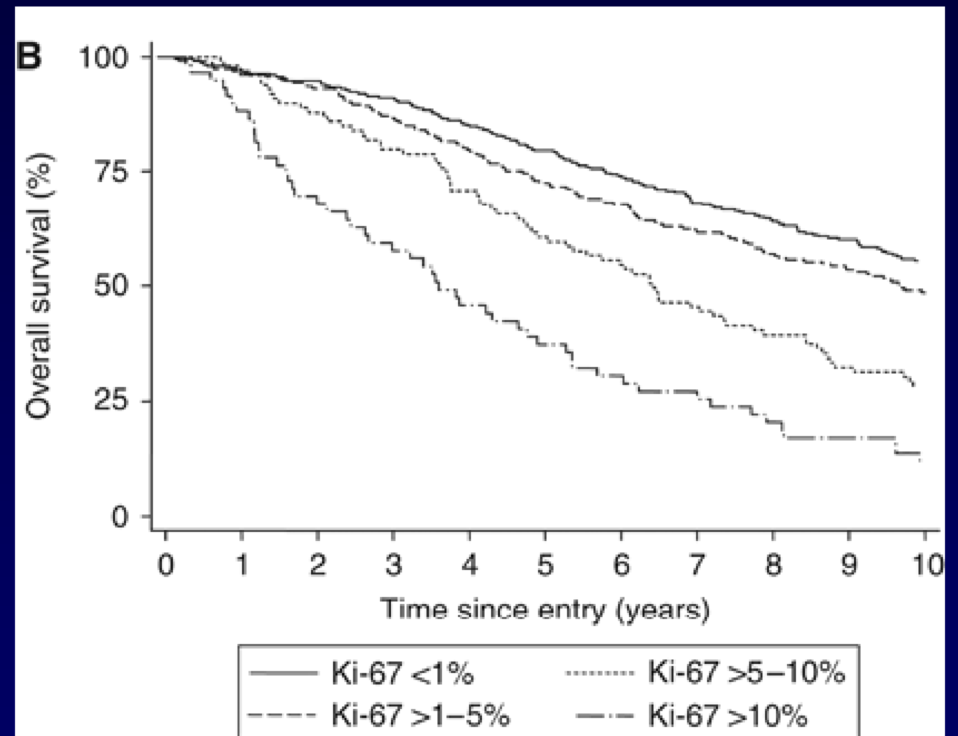
Distribution of Ki-67 in Different Tumor Areas in the Prostatectomy Specimen



Khatami A, et al. *Scand J Urol Nephrol.* 2009;43(1):12-18.

Prostate Cancer Survival And Overall Survival As Predicted By Four Groups Of Ki-67 Score





Berney DM. et al. *Brit J Cancer.* 2009;100(6):888-893.

Harrel's Concordance Index

- ...is the probability that, given 2 randomly selected patients, the patient with the worse outcome is, in fact, predicted to have a worse outcome.
- How accurate is the best prediction model that contains the new marker relative to the best model that lacks it? – That is, how much does the c-index improve with the knowledge of the patient's novel marker?

Accuracy analysis:

100% = perfect prediction
50% = toss of a coin

Kattan MW. *J Natl Cancer Inst.* 2003;95(9):634-635.

MSKCC Nomogram

63-year-old patient
PSA:11 ng/mL
T2b -Tumor
5 of 12 cores positive
Gleason score: 7 (4+3)

CURRENT MODEL	HISTORICAL MODEL	
Extent of Disease Probability		
Indolent Cancer		N/A
Organ Confined Disease		28%
Extracapsular Extension		60%
Seminal Vesicle Invasion		35%
Lymph Node Involvement		5.5%
Primary Treatment Outcome		
Progression Free Probability after Radical Prostatectomy	5 Year	81%
	10 Year	73%
Probability of Progression		
Metastases Probability after Conformal Radiation Therapy	5 Year	10%
	8 Year	17%

Memorial Sloan-Kettering Cancer Canter. Prostate Cancer Nomograms: Pre-Treatment. Memorial Sloan-Kettering Cancer Center Web site. 2009. Available at: http://www.mskcc.org/applications/nomograms/prostate/PreTreatment.aspx. Accessed October 13, 2010.

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Primary Treatment Outcome		
Progression Free Probability with External Beam Radiation Therapy	5 Year	N/A
Probability of Progression		
Metastases Probability after Conformal Radiation Therapy	5 Year	10%
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Memorial Sloan-Kettering Cancer Canter. Prostate Cancer Nomograms: Pre-Treatment. Memorial Sloan-Kettering Cancer Center Web site. 2009. Available at: http://www.mskcc.org/applications/nomograms/prostate/PreTreatment.aspx. Accessed October 13, 2010.

PARTIN-Tables

Based upon PSA, Gleason Score, and Clinical Staging, a probability is calculated for each of the following four: **Organ Confined Disease**, **Extraprostatic Extension**, **Seminal Vesicle Invasion**, and **Lymph Node Invasion**

Select:

PSA: >10 ng/ml **Gleason Score:** 4+3=7

Clinical Stage: T2b/c

Calculate Clear

Danil V, et al. The Partin Tables. James Buchanan Brady Urological Institute Johns Hopkins Medicine Web site. 2010. Available at: http://urology.jhu.edu/prostate/partintables.php. Accessed October 13, 2010.

PARTIN-Tables

Based upon PSA, Gleason Score, and Clinical Staging, a probability is calculated for each of the following four: **Organ Confined Disease**, **Extraprostatic Extension**, **Seminal Vesicle Invasion**, and **Lymph Node Invasion**

Select:

PSA: >10 ng/ml **Gleason Score:** 4+3=7

Clinical Stage: T2b/c

Organ confined: 11 (7-15)
Extraprostatic extension: 40 (30-52)
Seminal Vesicle Invasion: 19 (10-29)
Lymph Node Invasion: 29 (15-44)

All numbers represent predictive probabilities with a 95 percent confidence interval; ellipses indicate lack of sufficient data to calculate probability.

Danil V, et al. The Partin Tables. James Buchanan Brady Urological Institute Johns Hopkins Medicine Web site. 2010. Available at: http://urology.jhu.edu/prostate/partintables.php. Accessed October 13, 2010.

HAN-Tables

1.Preoperative model (For men who are considering surgery for prostate cancer, but have not had surgery yet)

Prediction of recurrence probability following surgery using the available information ***BEFORE*** the surgery (PSA level, biopsy Gleason score, and clinical stage)

Based upon PSA, Gleason Score, and Clinical Stage, **recurrence probability is calculated at 3, 5, 7, and 10 years following surgery**

Select:

PSA: 10.1-20 ng/ml **Gleason Score:** 4+3=7

Clinical Stage: T2b/c

Calculate Clear

Han M, et al. The Han Tables. James Buchanan Brady Urological Institute Johns Hopkins Medicine Web site. Available at: http://urology.jhu.edu/prostate/hanTables.php. Accessed: October 13, 2010.

HAN-Tables

1.Preoperative model (For men who are considering surgery for prostate cancer, but have not had surgery yet)

Prediction of recurrence probability following surgery using the available information ***BEFORE*** the surgery (PSA level, biopsy Gleason score, and clinical stage)

Recurrence Probability Following Radical Prostatectomy (by Han Table)

Probability of Biochemical Recurrence (detectable PSA level) at

3 years after surgery: 16% (5-44)
5 years after surgery: 25% (8-63)
7 years after surgery: 33% (11-76)
10 years after surgery: 41% (14-85)

All numbers represent predictive probabilities with a 95 percent confidence interval

Han M, et al. The Han Tables. James Buchanan Brady Urological Institute Johns Hopkins Medicine Web site. Available at: http://urology.jhu.edu/prostate/hanTables.php. Accessed: October 13, 2010.

Probability

	MSKCC Current	Partin	MSKCC Historical
Organ-Confined Disease	28%	11%	15%
Extracapsular Extension	60%	40%	45%
Seminal Vesicle Invasion	35%	19%	22%
Lymph Node Involvement	5.50%	29%	18%

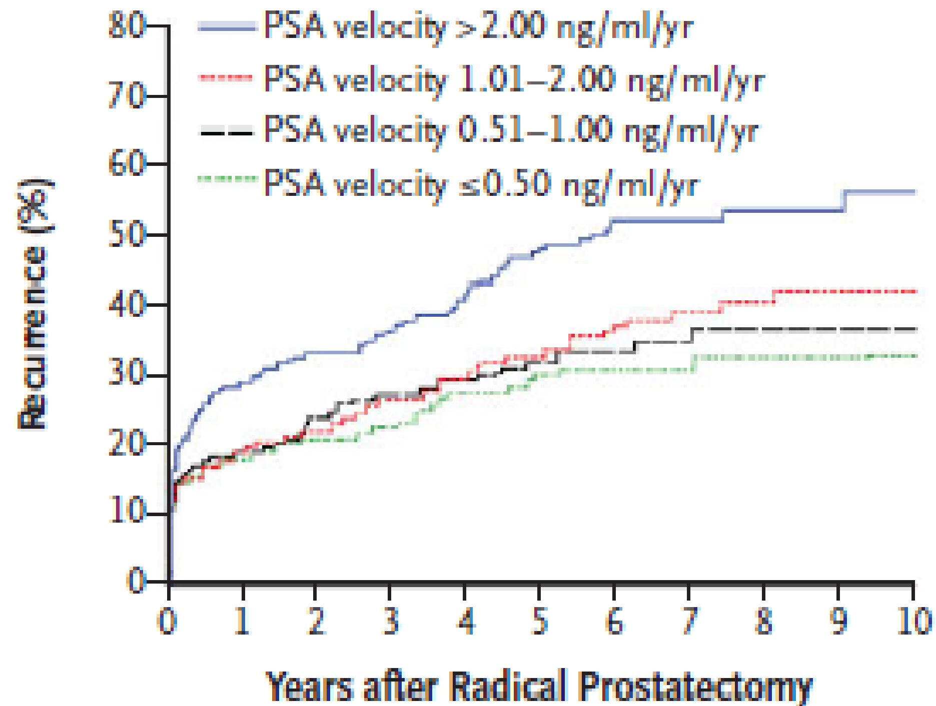
Memorial Sloan-Kettering Cancer Canter. Prostate Cancer Nomograms: Pre-Treatment. Memorial Sloan-Kettering Cancer Center Web site. 2009. Available at: http://www.mskcc.org/applications/nomograms/prostate/PreTreatment.aspx. Accessed October 13, 2010.
Danil V, et al. The Partin Tables. James Buchanan Brady Urological Institute Johns Hopkins Medicine Web site. 2010. Available at: http://urology.jhu.edu/prostate/partintables.php. Accessed October 13, 2010.

PSA-Velocity Definitions

Definition	Method	Start PSA	End PSA	Minimum No. of PSA Values	Maximum No. of PSA Values	Interval between PSA Values (months)
Velocity						
MSKCC	Slope	First	Last	2	All	NA
Thompson et al	Slope of log PSA	Study entry	Within 3 years	2	All	No
D'Amico et al	Linear regression	Within 1 year of diagnosis	Last before diagnosis	NA	All	NA
Sengupta et al	Slope	2 years before RP	NA	2	All	≥ 3
Rozhansky et al	Linear regression	Study entry	Within 6 months	2	NA	NA
Thiel et al	Linear regression	Before biopsy	At biopsy	2	All	≥ 12
Smith et al	Slope of log PSA	Study entry	8 months	3	3	4
D'Amico et al	Linear regression	Within 1 year of diagnosis	Last before diagnosis	2	3	≥ 6

O'Brien MF, et al. *J Clin Oncol.* 2009;27(22):3591-3597.

Preoperative PSA-Velocity and Risk of Recurrance

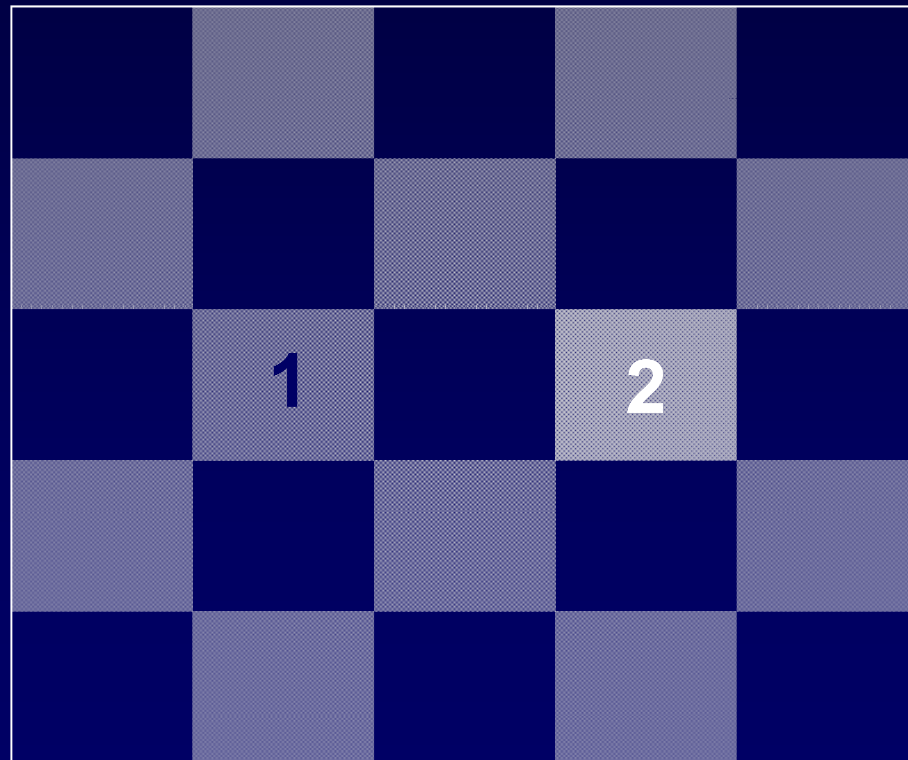


No. at Risk

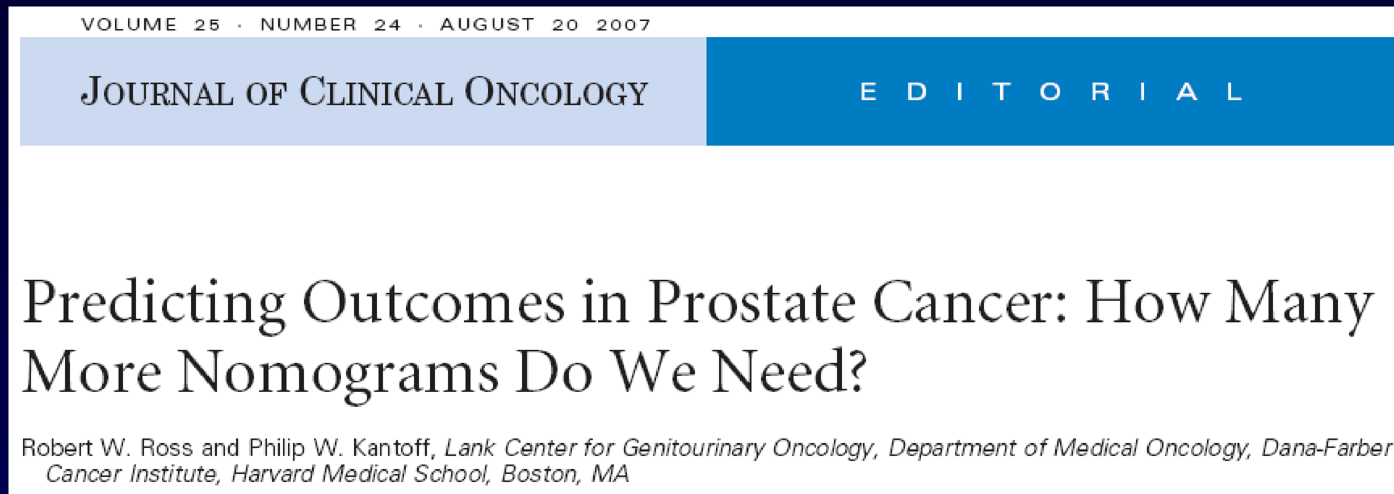
PSA velocity >2.00 ng/ml/yr	247	173	155	132	104	81	60	45	31	19	13
PSA velocity 1.01–2.00 ng/ml/yr	280	218	191	167	133	101	84	56	36	19	15
PSA velocity 0.51–1.00 ng/ml/yr	287	226	193	158	120	92	64	36	23	14	9
PSA velocity ≤0.50 ng/ml/yr	249	190	156	128	103	84	58	43	24	13	5

D'Amico AV, et al. *N Engl J Med.* 2004;351(2):125-135.

Which Square is the Darker One?



How Many Nomograms Do We Need?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JOURNAL OF CLINICAL ONCOLOGY

EDITORIAL

Predicting Outcomes in Prostate Cancer: How Many More Nomograms Do We Need?

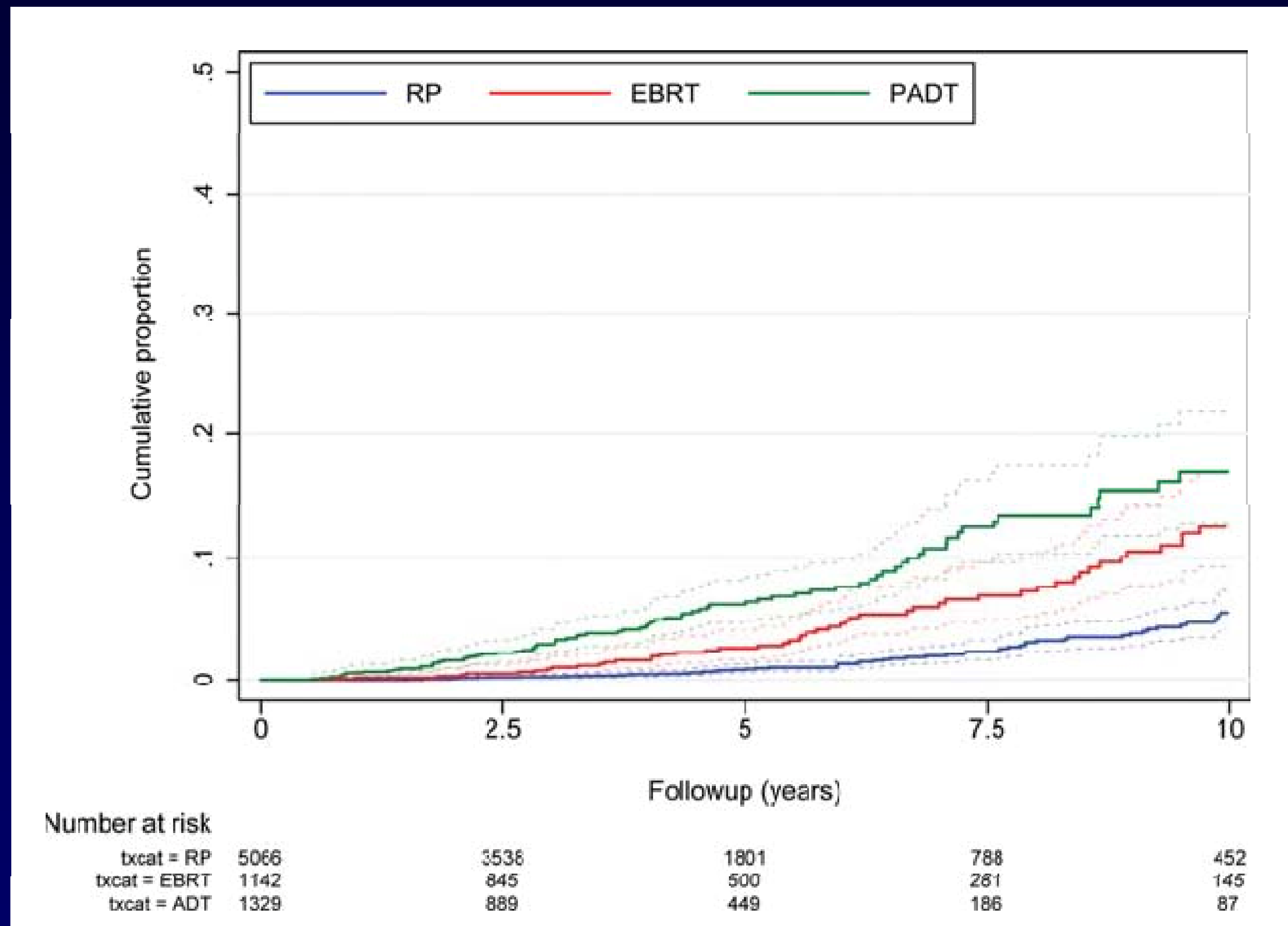
Robert W. Ross and Philip W. Kantoff, *Lank Center for Genitourinary Oncology, Department of Medical Oncology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA*

- **Is the question relevant to my practice?**
- **Is the patient population relevant to my practice?**
- **Is the nomogramm simple and useable?**
- **Has the nomogram been validated?**

"However, no nomogram will ever take the place of good clinical judgement and the well-informed patient."

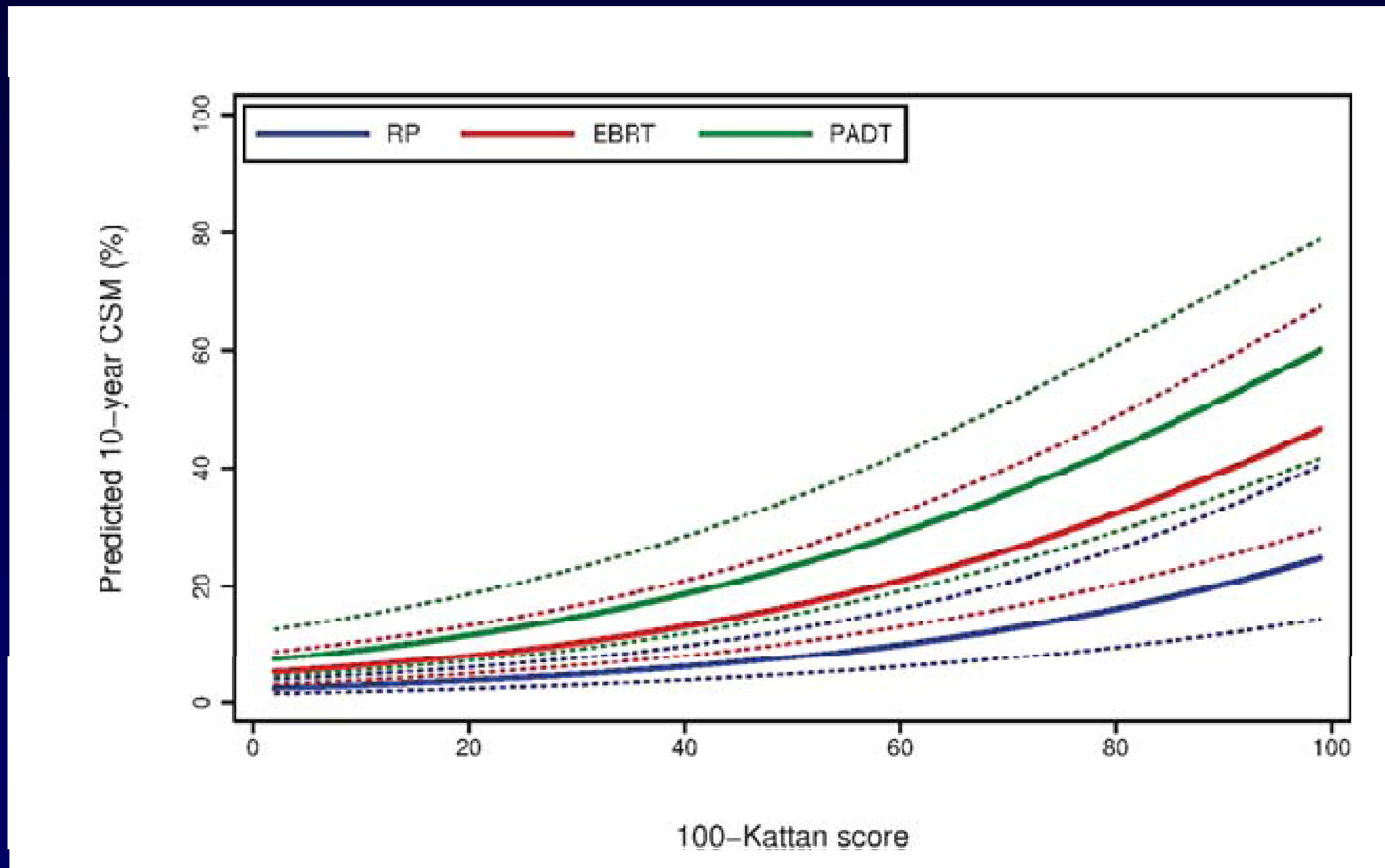
Ross RW, et al. *J Clin Oncol.* 2007;25(24):3563-3564.

Likelihood of PCa-Specific Mortality According to Primary Treatment



Cooperberg MR, et al. *Cancer.* 2010 Aug 5 [epub ahead of print].

Predicted 10-Year Cancer-Specific Mortality in Various Treatments



Cooperberg MR, et al. *Cancer.* 2010 Aug 5 [epub ahead of print].

Results of Survival Analysis

PCa-CSM

Variable	Kattan Score		
	HR[a]	*P*	95% CI
Age	0.98	.041	0.96-1.00
Risk points[b]	1.03	<.001	1.02-1.03
RP	Ref		
EBRT	2.21	<.001	1.50-3.24
PADT	3.22	<.001	2.16-4.81

ACM

Variable	Kattan Score		
	HR[a]	*P*	95% CI
Age	1.04	<.001	1.03-1.05
Risk points[b]	1.01	<.001	1.00-1.01
Comorbidity	1.12	<.001	1.07-1.18
RP	Ref		
EBRT	1.59	<.001	1.33-1.90
PADT	2.23	<.001	1.89-2.75

a HRs for age, comorbidity count, and risk points are given for each 1-year or 1-point increase, respectively. HRs for EBRT and PADT are given relative to RP.

b Risk points refer to Kattan or CAPRA scores.

HR: hazard ratio; CI: confidence Interval; RP: radical prostatectomy; Ref: reference category; EBRT: external beam radiation; PADT: primary androgen-depriviation therapy

Cooperberg MR, et al. *Cancer.* 2010 Aug 5 [epub ahead of print].

Artificial Increase of Kattan Score

Table 5. Hazard Ratios With 95% Confidence Intervals for Cancer-Specific Survival in the External-Beam Radiotherapy and Primary Androgen-Deprivation Therapy Groups Relative to the Radical Prostatectomy Group Controlling for Age and Kattan Score[a]

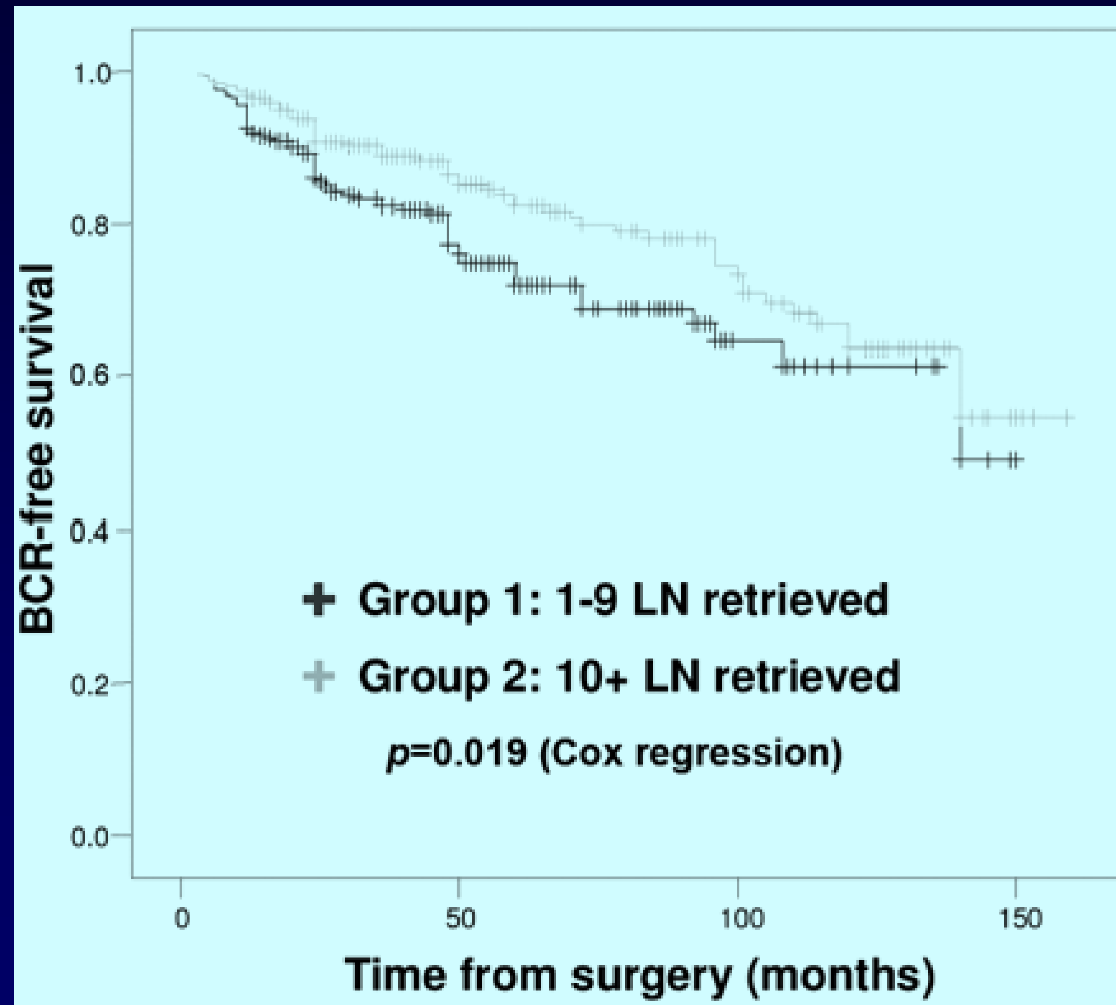
Increase in Kattan Score for RP Patients	HR (95% CI)	
	EBRT	PADT
0	2.21 (1.50-3.24)	3.22 (2.16-4.81)
5	1.95 (1.32-2.88)	2.84 (1.89-4.27)
10	1.72 (1.15-2.55)	2.50 (1.64-3.80)
15	1.51 (1.01-2.27)	2.20 (1.43-3.39)
20	1.33 (0.88-2.02)	1.94 (1.25-3.02)
25	1.17 (0.77-1.80)	1.71 (1.08-2.70)
30	1.03 (0.67-1.61)	1.51 (0.94-2.41)
35	0.91 (0.58-1.44)	1.33 (0.81-2.16)

HR indicates hazard ratio; CI, confidence interval; RP, radical prostatectomy; EBRT, external-beam radiotherapy; PADT, primary androgen-deprivation therapy.

a The Kattan score for each patient who underwent prostatectomy was increased artificially by 0 to 35 points.

Cooperberg MR, et al. *Cancer.* 2010 Aug 5 [epub ahead of print].

Bcr-Free Survival in the Two LN Groups (Standard/Extended LA)



Schiavina R, et al. *Anticancer Res.* 2010;30(6):2297-2302.

EUROPEAN UROLOGY 55 (2009) 1037–1063

available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

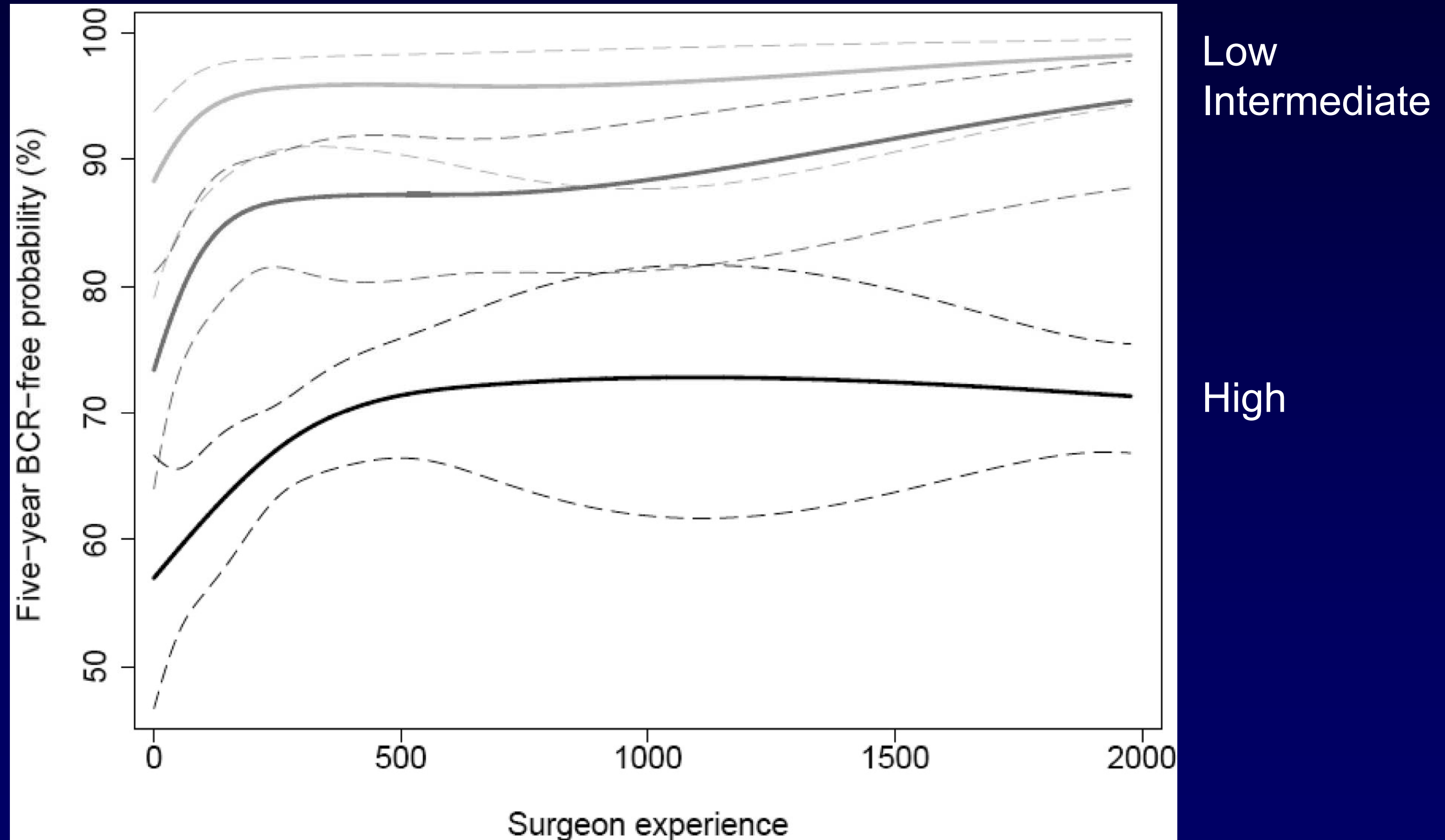
Review – Prostate Cancer

Retropubic, Laparoscopic, and Robot-Assisted Radical Prostatectomy: A Systematic Review and Cumulative Analysis of Comparative Studies

Vincenzo Ficarra [a,], Giacomo Novara [a], Walter Artibani [a], Andrea Cestari [b], Antonio Galfano [a], Markus Graefen [c], Giorgio Guazzoni [b], Bertrand Guillonneau [d], Mani Menon [e], Francesco Montorsi [f], Vipul Patel [g], Jens Rassweiler [h], Hendrik Van Poppel [i]*

"….but the available data were not sufficient to prove the superiority of any surgical approach in terms of functional and oncologic outcomes. Further high-quality, prospective, multicentre, comparative studies are needed."

Learning Curve for Cancer Control After RPE Stratified By Preoperative Risk Groups



Klein EA, et al. *J Urol.* 2008;179(6):2212-2217.

Effects of Surgeon Experience On Outcome by Preoperative Risk Group in 5,038 Patients

Risk Analysis	Surgeon Experience Adjusted *P* Value	Adjusted % 5-Yr Recurrence Probability		10 vs 250 Prior Case Difference	
		10 Prior Cases	250 Prior Cases	% Absolute	Relative
Overall:					
Low	<0.001	11.0	4.4	6.6 (3.4-10.3)	2.5 (1.7-4.0)
Intermediate	<0.001	25.4	13.4	12.0 (6.9-18.2)	1.9 (1.5-2.6)
High	0.016	42.6	32.9	9.7 (1.2-18.2)	1.3 (1.03-1.6)
After 1995:					
Low	0.008	10.3	2.2	8.1 (2.7-12.8)	4.7 (2.2-11.8)
Intermediate	<0.001	27.1	10.4	16.7 (7.6-25.1)	2.6 (1.7-4.3)
High	0.001	46.3	19.5	26.8 (11.6-43.4)	2.4 (1.5-3.8)

Klein EA, et al. *J Urol.* 2008;179(6):2212-2217.

PCa; cT2b cN0 M0, GS 7 (4 + 3); PSA 11; 5/6 Positive Biopsies of Right Lobe, Ki67—8%

Hyperlipidemia, controlled
65-year-old; sexually active

- ? External beam radiotherapy 75.6 Gy - 79 Gy (3D conformal or intensity modulated)
- ? External beam radiotherapy + brachytherapy
- ? External beam radiotherapy + androgen deprivation therapy (ADT)

Any Help From Nomograms?

- MSKCC:
- 78 Gy IMRT
  - without neoadjuvant HT:
    - 10-a-RFS 44%
  - with nHT :
    - 10-a- RFS 52%
- EBRT + BT : same as EBRT only

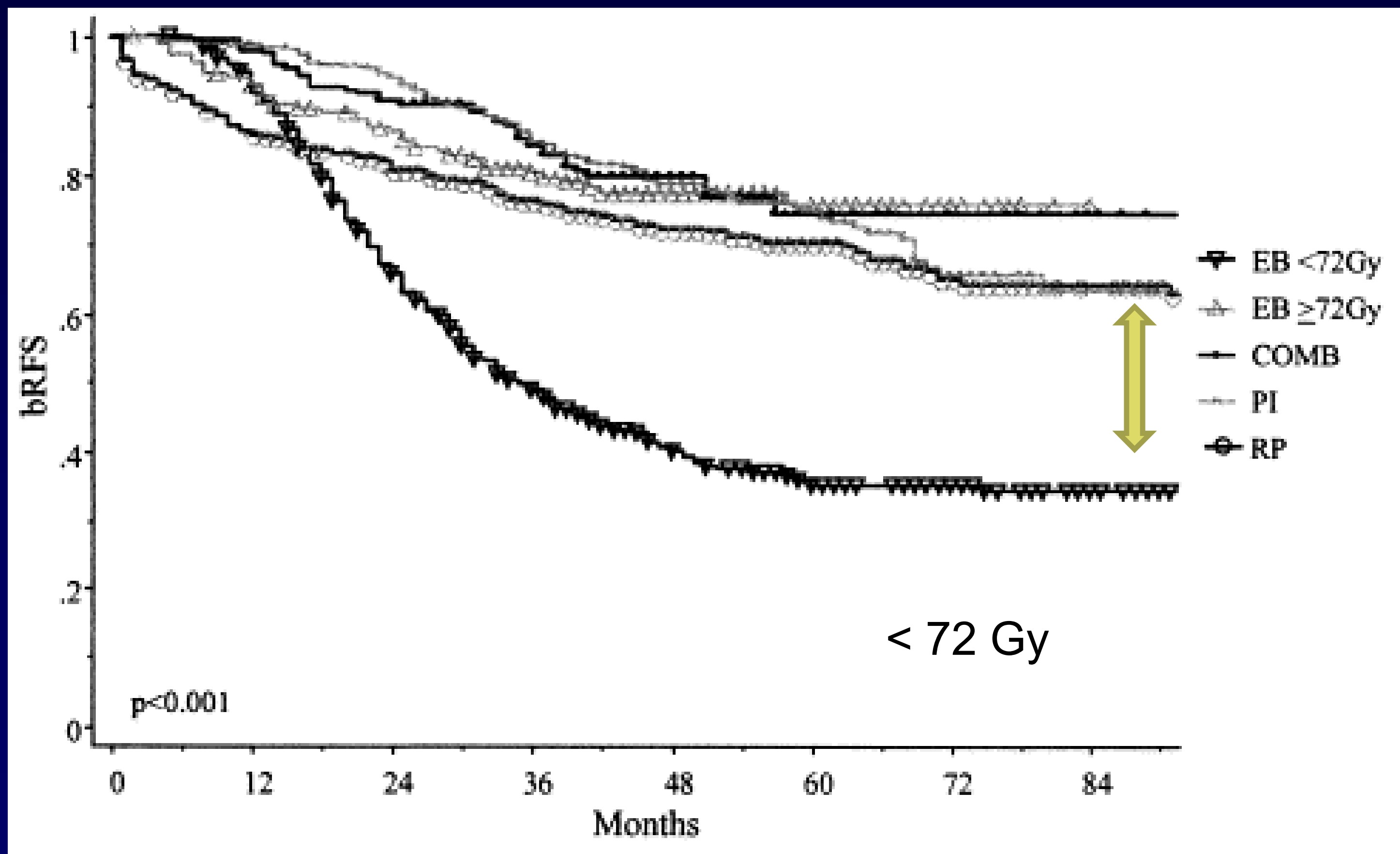
Memorial Sloan-Kettering Cancer Canter. Prostate Cancer Nomograms: Pre-Treatment. Memorial Sloan-Kettering Cancer Center Web site. 2009. Available at: http://www.mskcc.org/applications/nomograms/prostate/PreTreatment.aspx. Accessed October 13, 2010.

Does Dose Matter?

Multi-institution series on 2991 patients

bNED by treatment modality for **unfavorable-risk** pts.

RP, **EBRT <72 Gy, EBRT ≥72 Gy,** PI, or COMB.



Kupelian PA, et al. *Int J Radiat Oncol Biol Phys.* 2004;58(1):25-33.

Dose Matters!

- But *not necessarily* the method…
- In RT-Only settings:
  - biologic effective doses > 78 Gy to the prostate
- …achievable by EBRT (IGRT-IMRT)
- …as well as by Brachytherapy
- Provided that the target volume is appropriately covered !

What to Irradiate?

Partin Tables , Update 2005

Pathologic Stage	Probability % (range)
Organ-confined (N = 8)	11 (7-15)
Extraprostatic extension (N = 15)	40 (30-52)
Seminal vesicle (+) (N = 10)	19 (10-29)
Lymph node (+) (N = 8)	29 (15-44)

Makarov DV, et al. *Urology.* 2007;69(6):1095-1101.

Validation of a Biopsy-Based Pathologic Algorithim for Predicting Lymph Node Metastases in Patients with Clinically Localized Prostate Cancer

Gleason Score	LN Negative (%)	LN Positive (%)
≤ 3+3	98.8	1.2
3+4	88.7	11.3
4+3	86.3	13.7
4+4	60.0	40.0

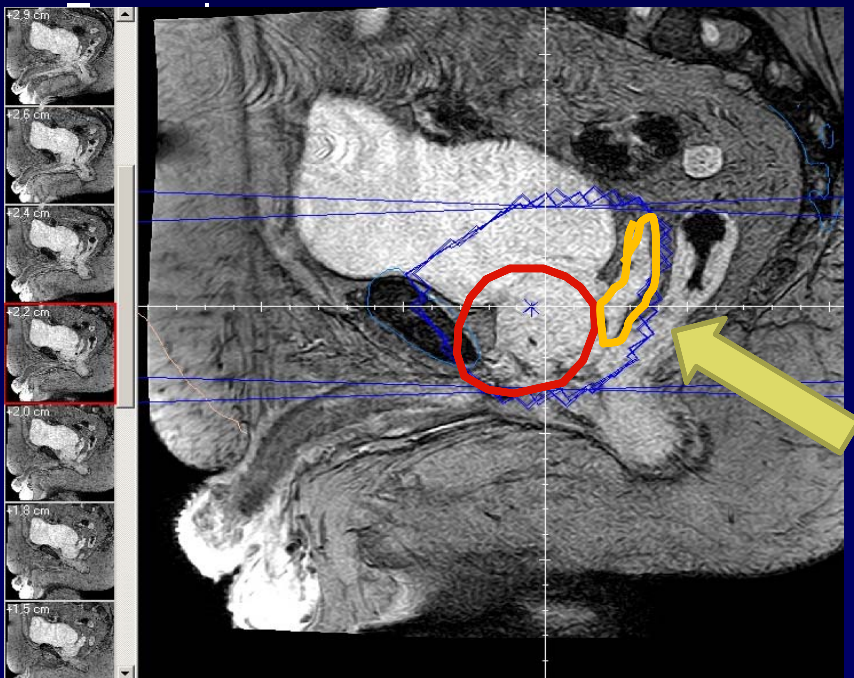
MSKCC -Nomogram: 5.5%
Roach-Formula: 17.3 %
Average: 16.38 %

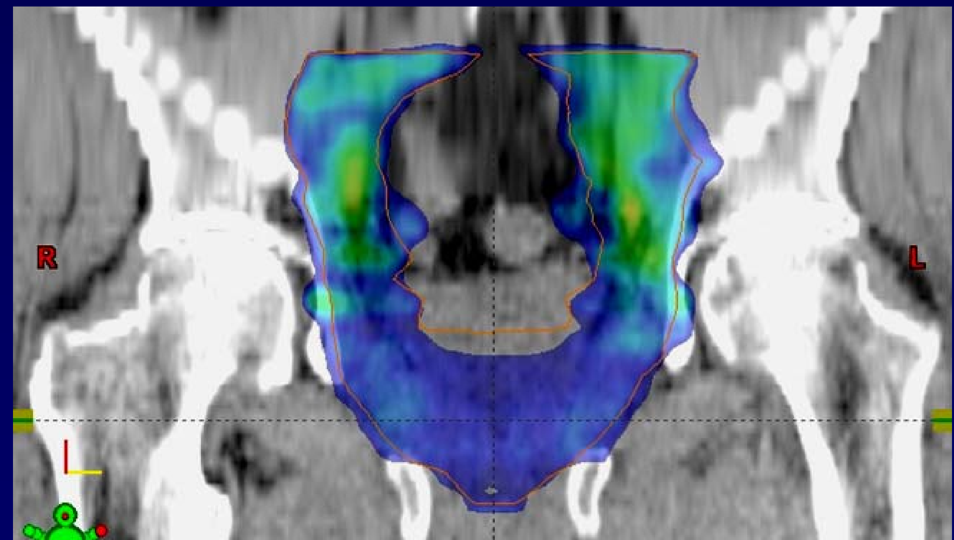
Haese A, et al. *Cancer.* 2002;95(5):1016-1021.

What to Irradiate?

- Prostate plus pelvic lymph nodes (>15%)
- Targeting for prostate includes SV

Risk of lymph node involvement:





PCa; cT2b cN0 M0, GS 7 (4 + 3); PSA 11; 5/6 Positive Biopsies of Right Lobe, Ki67—8%

Hyperlipidemia, Controlled
65-Year-Old; Sexually Active

- External beam radiotherapy 75.6 Gy - 79 Gy (3D conformal or intensity-modulated) ✓
- ? External beam radiotherapy + brachytherapy
- ? External beam radiotherapy + androgen deprivation therapy (ADT)

Intermediate-Risk PCa – Also Candidates for BT?

- BT only bears risk of underdosage in regions of extracapsular spread (incl. SV, NII.) ➔ *Combination with EBRT*
- Critz 2000: LDR-Brachy plus 45 Gy EBRT
  - 144 pts with PSA 10-20
  - 4-a-bNED 75%
- Sylvester 2007: 45 Gy EBRT plus LDR-BT
  - 15-a bNED rates for intermediate-risk pts: 80%

Critz FA, et al. *J Urol.* 2000;164(3 Pt1):738-741. Sylvester JE, et al. *Int J Raiat Oncol Biol Phys.* 2007;67:57-64.

Dose Escalation by Brachytherapy: HDR-Boost Ir-192

- Frequently administered with EBRT 45 – 50 Gy as boost to bulky tumors
- Pisansky 2008:
  - Review 12 studies / >5700 pts
  - Actuarial 5-10 y survival rates for low-risk, intermediate-risk, and high-risk disease ranged from 93 to 100, 88 to 100, and 62 to 97 percent, respectively
- No established role, iso-efficacy likely, superiority towards high-dose EBRT unclear

Pisansky TM, et al. *Mayo Clin Proc.* 2008;83(12):1364-1372.

PCa; cT2b cN0 M0, GS 7 (4 + 3); PSA 11; 5/6 Positive Biopsies of Right Lobe, Ki67—8%
Hyperlipidemia, Controlled
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- **External beam radiotherapy 75.6 Gy - 79 Gy (3D conformal or intensity modulated) ✓**
- **External beam radiotherapy + brachytherapy ✓**
- **? External beam radiotherapy + androgen deprivation therapy (ADT)**

Subgroup Analysis From RTOG 8610 and RTOG 9202

- **Short-term-neoadjuvant + concomitant HT leads to better outcome in most endpoints**

  (OS only increased in GS <7)

- **Additional adjuvant HT (2 a) has positive impact only in GS >7**

- **GS 7 Tumor: T1,2 profit from short-term HT, T3 profit from long-term HT**

  RTOG Metaanalysis BCJ 2004

Gottschalk AR, et al. *Br J Cancer.* 2004;90(5):950-954.

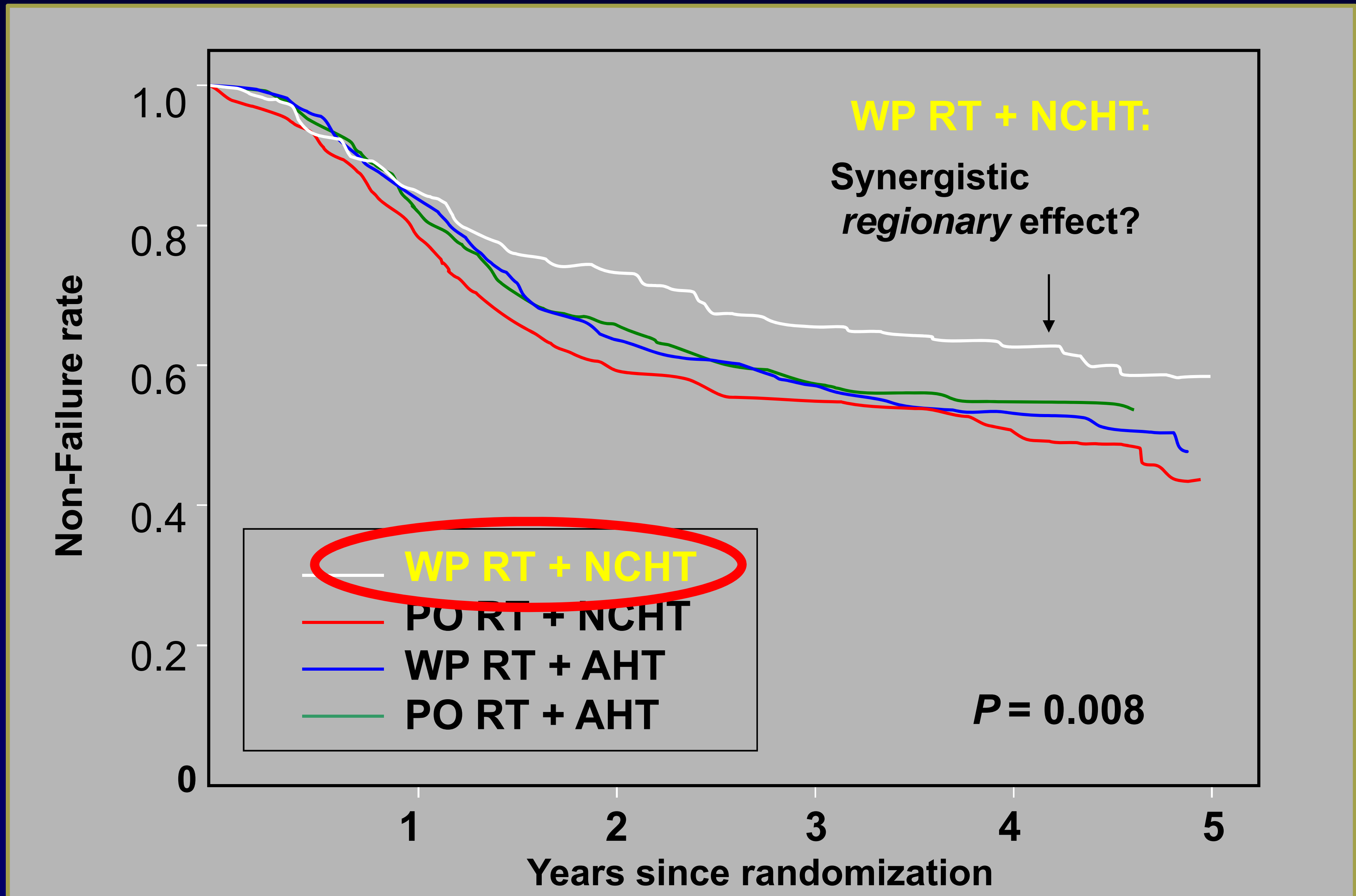
HT-Sequencing and Role of Pelvic RT? RTOG 9413

Study	Treatment	Locoreg. Control	Distant metastasis	bNED-S	OAS
RTOG 9413 (Roach 2003) T1c-T4, PSA < 100 Estimated risk of LN Involvement >15 %	WP + NCHT WP + AHT PO + NCHT PO + AHT	4-year **9.1 WP** v 8.0 PO ($P = 0.78$)	4-year **8.2 WP** v 6.6 PO ($P = 0.54$)	4-year **69.7** 63.3 57.2 63.5 **($P = 0.048$)**	4-year 84.7 v 84.3 ($P = 0.94$)

WP: Whole Pelvis; PO: Prostate only
NCHT: neoadjuvant/concomitant; AHT: adjuvant (4 Mo MAB)

Roach M III, et al. *J Clin Oncol.* 2003;21(10):1904-1911.

RTOG 9413: Progression-Free Survival



Lawton CA, et al. *Int J Radiation Oncol Biol Phys*. 2007;69(3):646-655.

How Useful is *Short-Term* Hormo-Radiation for Intermediate-Risk PCa ?

RTOG 94-08

NHT for "smaller" tumors
T1b-2b, PSA ≤ 20

RT alone 66, 6 Gy
vs
NHT (TAB) x 4 months + RT

- **987 pts HRT, 992 pts RT; med FU>8 a**
- **Estimated OS at 12 y:**
  - **51% for H+RT**
  - **46% for RT arm (*P* = 0.03)**
- **Neg. prognostic impact GS≥7**

Problem: insufficient dosage, contribution of HT to "appropriate" EBRT with 74-78 Gy?

McGowan D, et al. Presented at: 2010 Genitourinary Cancer Symposium; March 5-7, 2010: San Francisco, California. Abstract 6.

Risk-Adapted (H)RT

		bNED
Low Risk <T2b, GS < 7; PSA < 10	RT-only: XRT (74 Gy +) or BT Optional: neoadj. AB (BPH)	80%-90% (7a)
Intermediate Risk Tx, GS 7, PSA > 10	Neoadj. MAB (3 Mo) **XRT 74-78 Gy** +/ - short term AB (LHRH 6 Mo)	60-80 (+?) % (5a) *(70Gy)*
High Risk GS 7-10, T2b-T3, “bulky tumors” PSA > 20	Neoadj. MAB (3 Mo) XRT 74 (-78) Gy + long term AB (LHRH 24-36 Mo)	50% (10a) (70 Gy)

EBRT Versus Radical Prostatectomy
Morbidity?

- No randomized trials, large observational series
- Urinary incontinence less than half
- Irritative bladder symptoms similar
- Irritative bowel complaints more common
- Sexual dysfunction:
  - 3 months after RPE nearly universal
  - improves gradually, especially in men <65 years
  - In contrast, sexual dysfunction is less common in the early months following RT
  - incidence increases over time

Potosky AL, et al. *J Natl Cancer Inst.* 2000;92(19):1582-1592.

PCa; cT2b cN0 M0, GS 7 (4 + 3); PSA 11; 5/6 Positive Biopsies of Right Lobe, Ki67—8%

Hyperlipidemia, Controlled
65-Year-Old; Sexually Active

- Radiotherapy with bioequivalent doses of 78 Gy (+) plus androgen deprivation therapy (ADT) in neoadjuvant/concomitant/short-term adjuvant setting

Do We Have to Treat PCa?

- 1 in 6 men >50yr receives diagnosis of PCa
- 1 in 33 men >50yr dies of PCa
- 4 in 5 men will not have clinically relevant progress
  - (age, comorbidities, favorable tumor biology)
- 1979 to 2002 PCa-incidence in men <65yr ⇧ 4.28-fold[1]
- 10 yr survival of grade I tumor > 90%[2]

1.Ries LA, et al (eds). *SEER Cancer Statistics Review, 1975-2002.* National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2002/, based on November 2004 SEER data submission, posted to the SEER Web site 2005. Accessed October 13, 2010.
2.Lu-Yao, et al. *Lancet.* 1997;349(9056):906-910.

Definitions of Insignificant or Low-Risk Prostate Cancer

Study	Definition	Study	Definition
Epstein et al & Bastian et al	Clinical stage T1c PSA density <0.15 ng/mL No Gleason pattern 4 or 5 <3 positive cores <50% cancer per core	Soloway et al	Clinical stage T2 or lower PSA level <15 ng/mL No Gleason pattern 4 or 5 <50% cancer per 2 positive cores
D'Amico et al	PSA level ≤10 ng/mL No Gleason pattern 4 or 5 Clinical stage T2a or lower	van den Bergh et al (PRIAS)	Clinical stage T1c-T2b No Gleason pattern 4 or 5 PSA density <0.20 ng/mL PSA level <10 ng/mL Fewer than 3 positive cores
Dall'Era et al	PSA level ≤10 ng/mL No Gleason pattern 4 or 5 Clinical stage T2a or lower PSA density <0.15 ng/mL <33% positive cores	van As et al	Clinical stage T1-T2a Gleason sum ≤7 (3 + 4) PSA level <15 ng/mL <50% of biopsy cores positive
Patel et al	Clinical stage T3 or lower Gleason sum ≤7	Dall'Era et al (commonly used criteria)	Gleason sum 6 No Gleason pattern 4 or 5 PSA level <10 ng/mL and stable PSA kinetics ≤50% single core involvement ≤33% positive cores

PSA=prostate-specific antigen; PRIAS=Prostate Cancer Research International Active Surveillance

Bastian PJ, et al. *Eur Urol.* 2009;55(6):1321-1330.

Indications for Active Treatment

Study	Treatment criteria	Median age, yr (range)	Percentage of pts w/ active treament, % (total no. pts)	Mortality (related to prostate cancer)	Median follow-up, mo
van As et al	PSAV >1 ng/mL per year Gleason score ≥4+3 or >50% cancer per core	67 (50-79)	20 (326)	None	22
Dall'Era et al	Gleason score ≥7 on rebiopsy, rising PSA, increase in volume by biopsy parameters	63.4 (40-86)	21 (321)	None	24
Carter et al	Gleaseon score ≥7 on rebiopsy, any pattern 4, 5 >2 cores involved, >50% any single score involved	65.7 (45.8-81.5)	31 (320)	None	23
Klotz et al	PSA DT <2 yr Gleason score ≥8 *Update* 2001: PSA DT <3 yr Gleason score ≥7 (4+3)	NA	34 (299)	None	64
Patel et al	Gleason score increase, PSAV >0.75/yr, increase DRE/TRUS detected lesion, increase biopsy volume	Mean: 65.3 (44-79)	35 (88)	None	44
Hardie et al	Rising PSA, clinical judgment	70.5 (59-81)	14 (80)	None	42
Roemeling et al	PSA DT	69.8 (25-75)	29 (278)	None	40
Ercole et al	Increase in tumor volume, Gleason score progression, urinary symptoms, change of DRE, patient preference	68 (52-75)	7.8 (40)	None	48
Soloway et al	Gleason score increase, PSA and PSA DT increase, stage progression, increase biopsy volume, patient preference	67 (mean: 66.02)	<1 (99)	None	45.3 (mean)

PSA DT = PSA doubling time; PSAV = PSA velocity; DRE = digital rectal examination; TRUS = transrectal ultrasound; NA = not available

Bastian PJ, et al. *Eur Urol.* 2009;55(6):1321-1330.