Radiobiology and Prognostic factors in Genito Urinary Malignancies

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Prognostic Factor

Practically, prognostic markers predict "the natural course of an individual cancer, distinguishing *good outcome* tumors from *poor outcome* tumors, and they guide the decision of whom to treat and/or how aggressively treated"

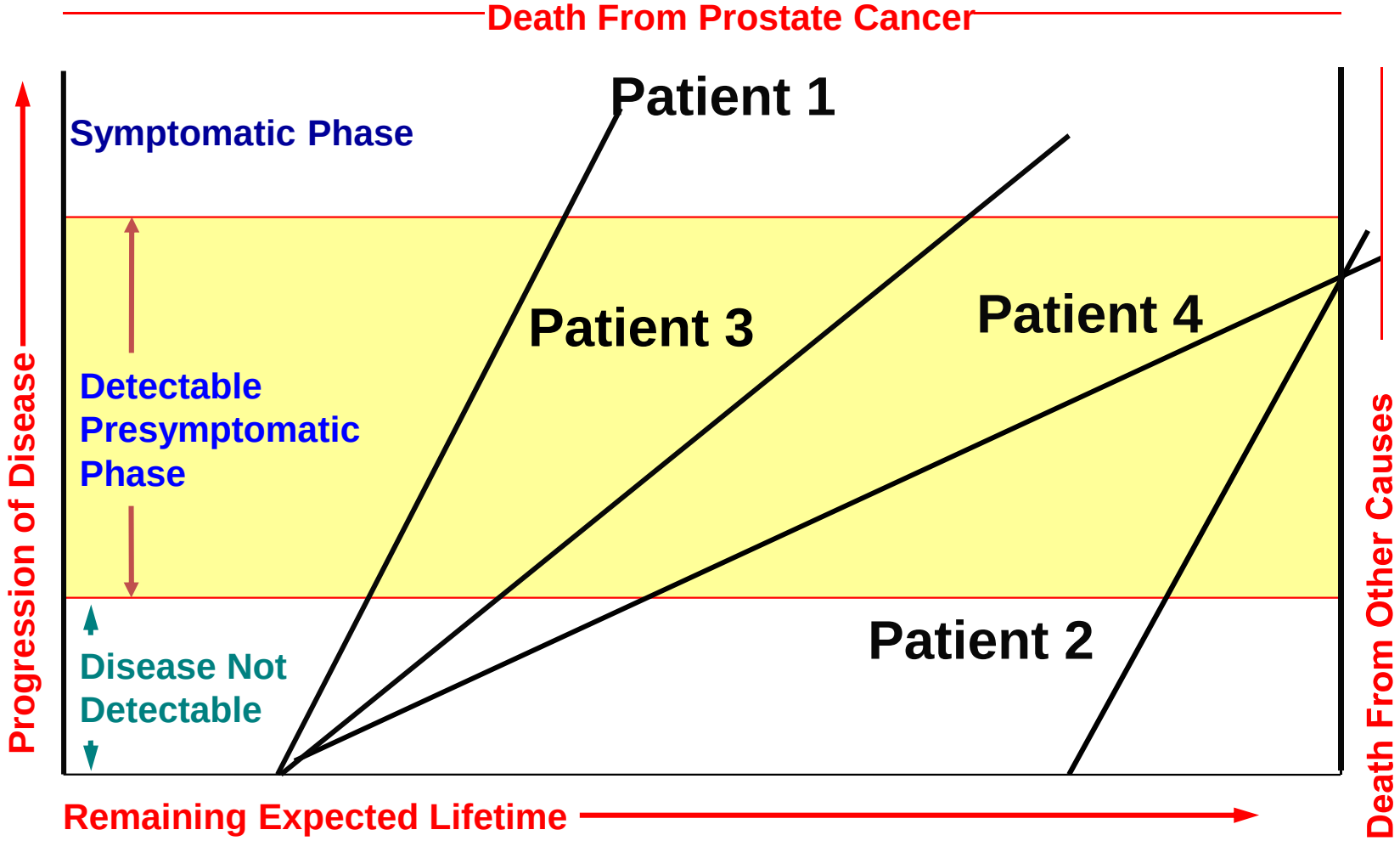
Predictive Factor

Predictive markers are molecules that "provide upfront information as to whether or not a patient is likely to benefit from a specific therapy" [Duffy

PROSTATE CANCER

Natural Course of the Disease

Prostate Cancers Vary in Their Natural Histories



Natural Course of the Disease

- **Clinically Significant**
  - **Will cause clinical manifestation**
  - **Will interfere in the life.**
  - **Likely to die of cancer**

- **Clinically Insignificant**
  - **Will not interfere in life**
  - **Likely to die with cancer and not of cancer**

Challenges of prostate cancer

- **Goal: Find *clinically significant* cancer at a point when a cure is possible**
- **Goal: Avoid excessively aggressive treatment in *clinically insignificant* disease**
- **Examine prognostic factors of diagnosed disease to predict if it will be significant**

Prognostic indicators

- **Clinico-pathological.**
- **Biological**
- **Proliferative Index**

Clinico-pathological

- History and Clinical examinations
- Blood test
- Radiology
- Biopsy
  - PSA
  - Stage
  - Grade
  - #positive biopsy cores
  - %biopsy core positive

This helps us predict what cancer may be
significant vs. insignificant

Age

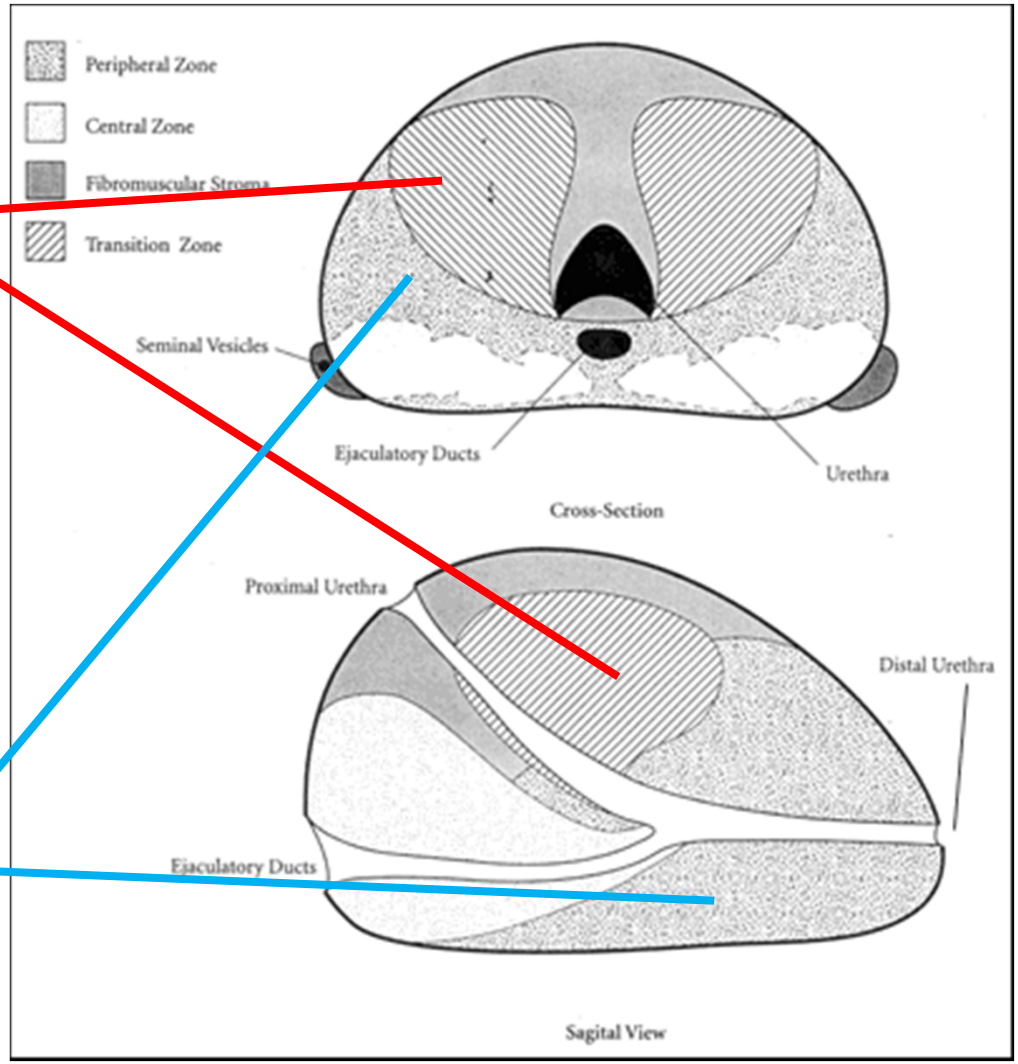
- **Controversial**
- **Enough evidence suggest patients with more than 65 years of age are more likely to have distant metastasis at 5 years after radical RT**
- **Younger patients have better outcome after radical prostatectomy.**

Volume

- **Debatable.**
- **Difficult to measure**
- **Higher volume is associated with capsular invasion, seminal vesicle invasion and nodal metastasis.**
- **In one of the study after radical prostatectomy, rule of 10% was observed**
  - **0.5 cc** **10% probability capsule invasion**
  - **4cc** **10% probability SV Invasion**
  - **5cc** **10% Probability Dist. Met**

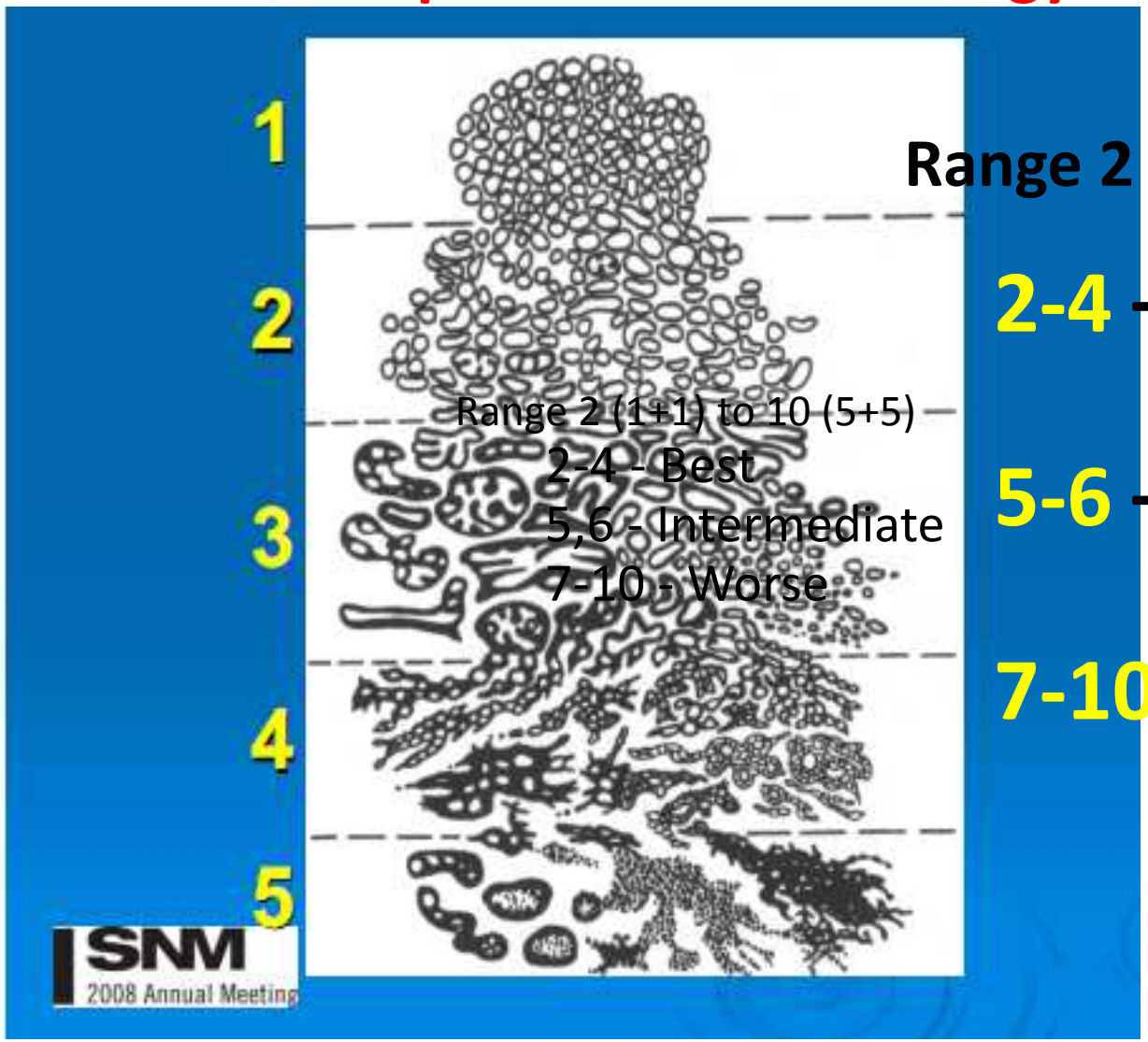
Zone of Origin

- Tumor arising from transitional zone are more likely to have favorable pathological features than tumor arising from peripheral zone



Gleason Grading

Based on two predominant histology.



Range 2 (1+1) to 10 (5+5)

2-4 – Best

5-6 – Intermediate

7-10 - Worse

What Does the Grade of the Tumor Predict?

Grade of a tumor is predictive of its likelihood to spread beyond confines of the prostate, affecting curability.

12% of low-grade tumors (2-4)
spread beyond prostate in 10 years
33% of medium-grade tumors (5,6)
spread beyond prostate in10 years
61% of high-grade tumors (7-10)
spread beyond prostate in 10 years

Sources: Mayo Clinic.com. *Prostate Cancer Guide*. Available at: http://www.mayoclinic.com/health/prostate-cancer/PC99999.
Prostate Cancer in California. Ed. Mill PK. Public Health Institute. 2000.

Gleason Grading

Prostate Cancer Gleason Score	Risk of death in 15 years
2 - 4	4 - 7 %
5	6 - 11%
6	18 - 30%
7	42 - 70%
8 - 10	60 - 87%

Albertson PC, et al. JAMA 1995; 274: 626-631

Prostate specific antigen (PSA)

- Protein produced by glandular tissue of prostate
- Present in small but measurable quantities in normal, healthy men
  - "normal" range increases with age
- Elevated PSA suggests
  - Benign hypertrophy
  - Recent ejaculation
  - Prostatitis/infection
  - Prostate cancer

Prostate specific antigen (PSA)

- **Normal Range** **0-4ng/ml**

- **Age specific PSA**

Age (years)	Recommended Reference Range for Serum PSA (ng/mL)
40–49	0.0–2.5
50–59	0.0–3.5
60–69	0.0–4.5
70–79	0.0–6.5

Prostate specific antigen (PSA)

PSA < 4ng/ml ***?Safe***

2004 Study of men: PSA never above 4ng/ml; no abnormal rectal exam

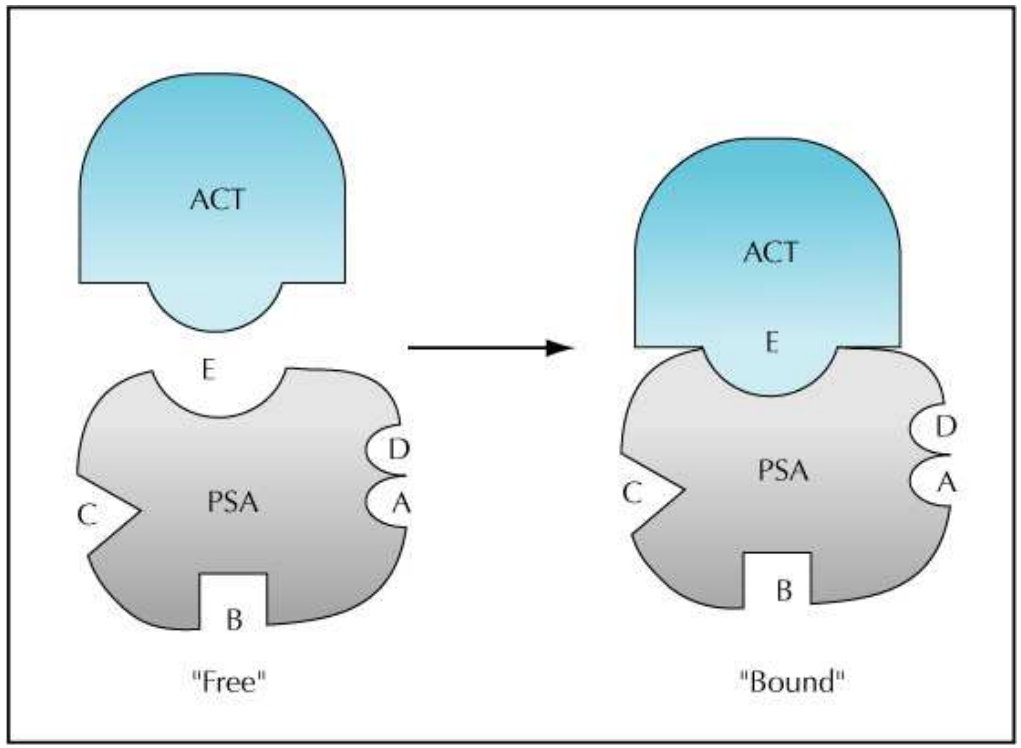
Percent with prostate cancer		PSA level (ng/ml)
26%	**15% of Patients may have Cancer**	3.1 to 4.0
24%		2.1 to 3.0
17%		1.1 to 2.0
10%		.6 to 1.0
7 %		less than .5

Sources: Cooner WH, Mosley BR, Rutherford CL Dr. et al. Prostate cancer detection in a clinical urological practice by ultrasonography, digital rectal examination and prostate specific antigen. *J Urol*. 1990;143:1146-52. Cited in Thompson IM, Pauler DK, Goodman PJ, Tangen CM, Lucia MS, et al.
Krumholtz JS, Carvalhal GF, Ramos CG, et al. Prostate-specific antigen cutoff of 2.6 ng/mL for prostate cancer screening is associated with favorable pathologic tumor features. *Urology*. 2002;60:469-473.

Prostate specific antigen (PSA)

- *PSA > 4 ng/ml ? Always Cancer.*
- PSA 4 – 10 ng/ml 25% will have Prostate ca.
- PSA > 10 ng/ml 50% will have Prostate ca.

Free and total prostate-specific antigen:

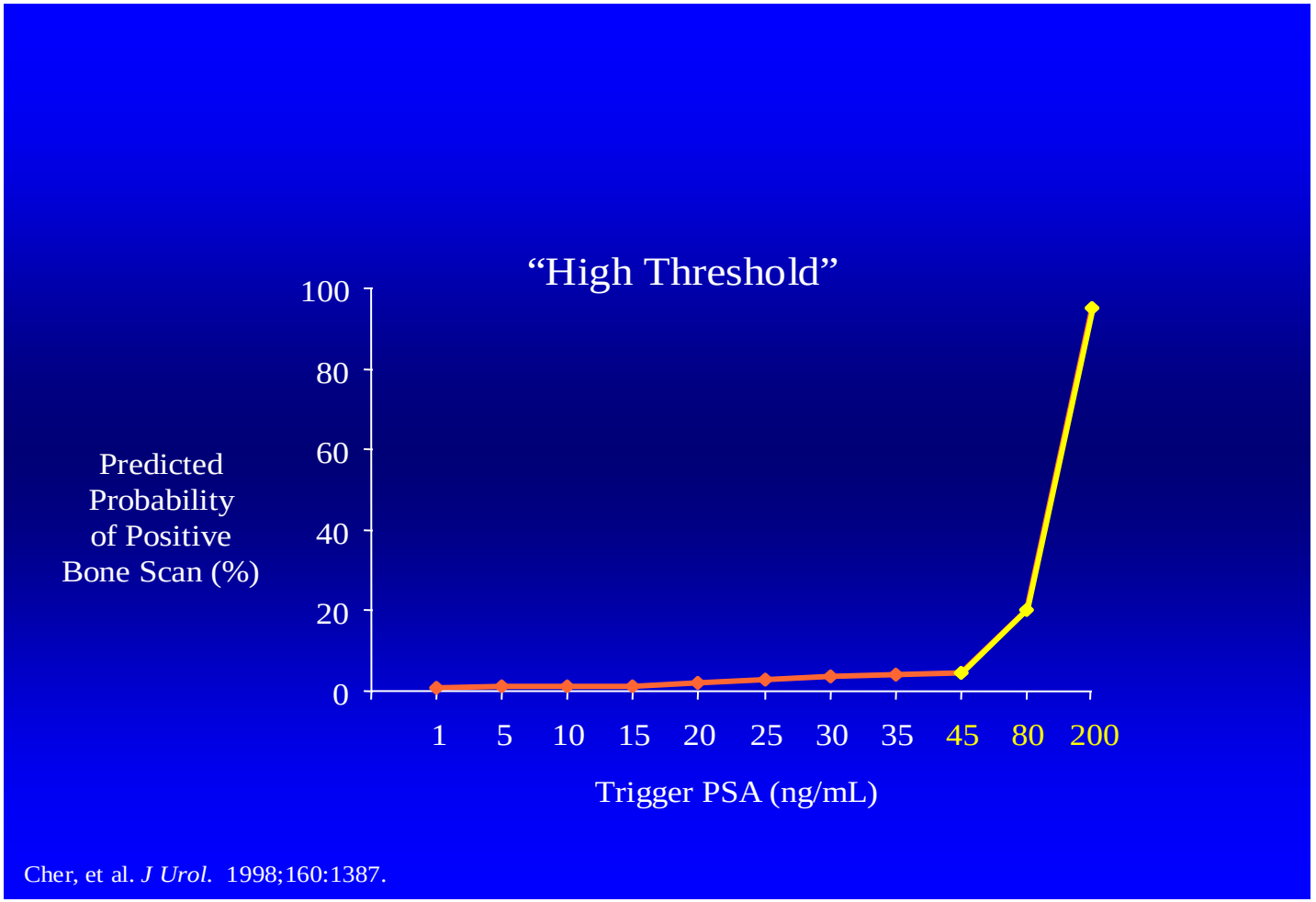


Less than 10%

Biopsy indicated

PSA as Prognostic

Bone Scans-limited usefulness with PSA<20



Cher, et al. *J Urol.* 1998;160:1387.

"High Risk" Factors for Lymph Node Metastases

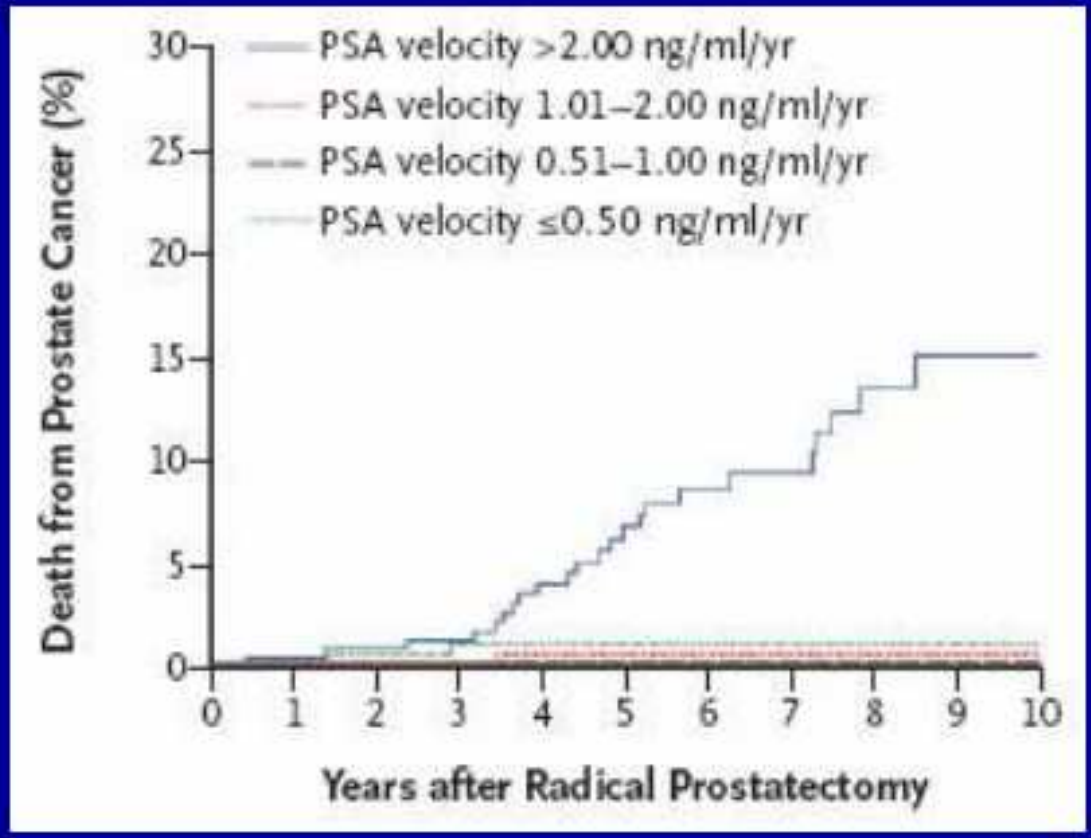
- Gleason Sum 7, PSA $\geq$ 10 ng/ml
- Gleason Sum 6, PSA $\geq$ 20 ng/ml

These currently utilized "high risk" factors significantly underestimate patients at risk for metastasis.

PSA Velocity

- Rate of rise over time.
- 20% annual increase.
- Absolute increase of 0.75 ng/ml/year.

PSA Velocity *Predicts P-Stage, Recurrence & Death*



PSA Velocity >2ng/mL significantly associated with:

LN metastases, high stage, high grade, shorter time to recurrence and death

Death rate from CaP of 9.2% within 7 years of RP

PSA doubling time (PSADT) as Prognostic factor

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Pretreatment prostate specific antigen doubling time as prognostic factor in prostate cancer patients

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Keywords: *prostate-specific antigen, prostate cancer, PSADT, PSA doubling time, education rate*

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All Patients

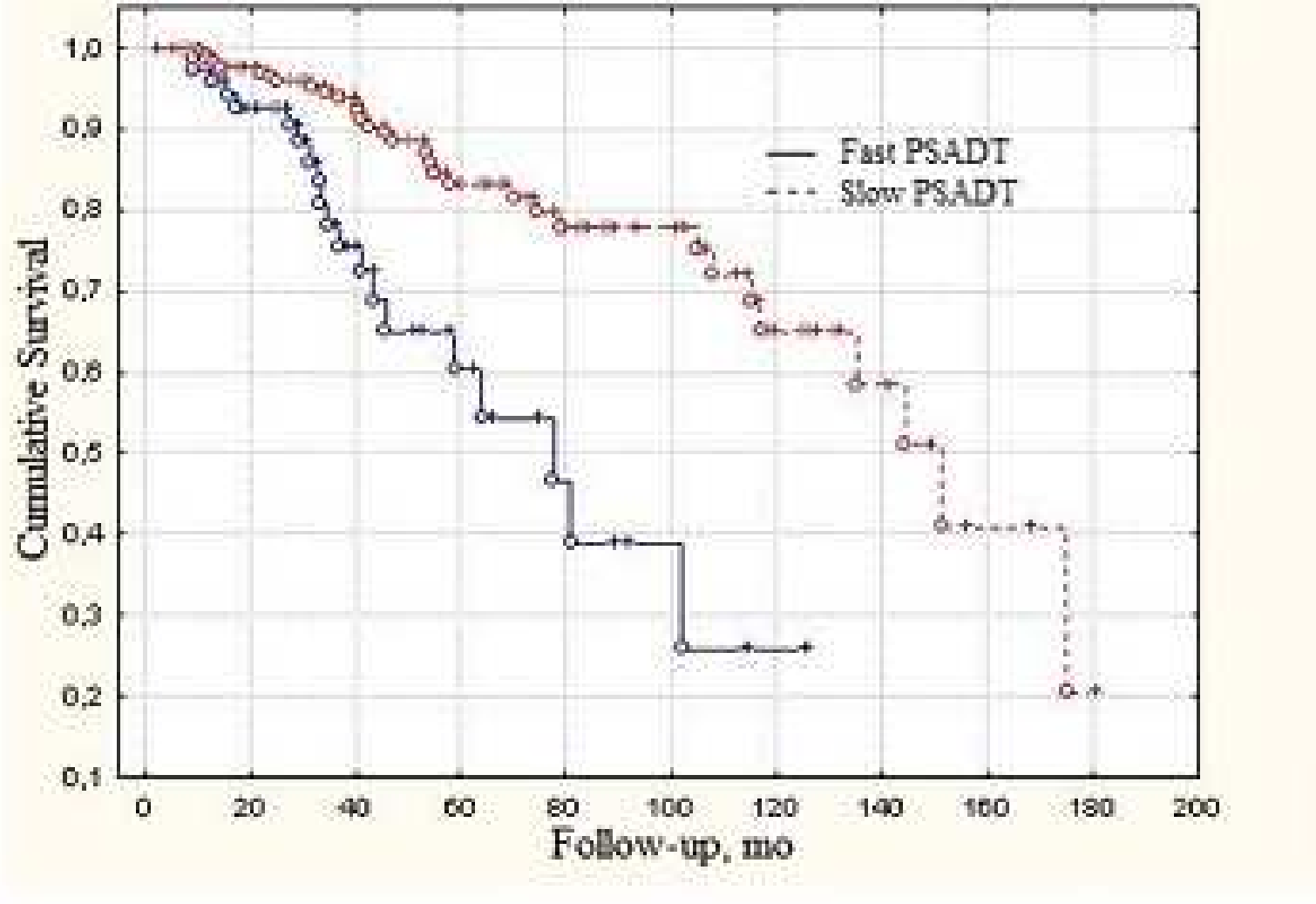
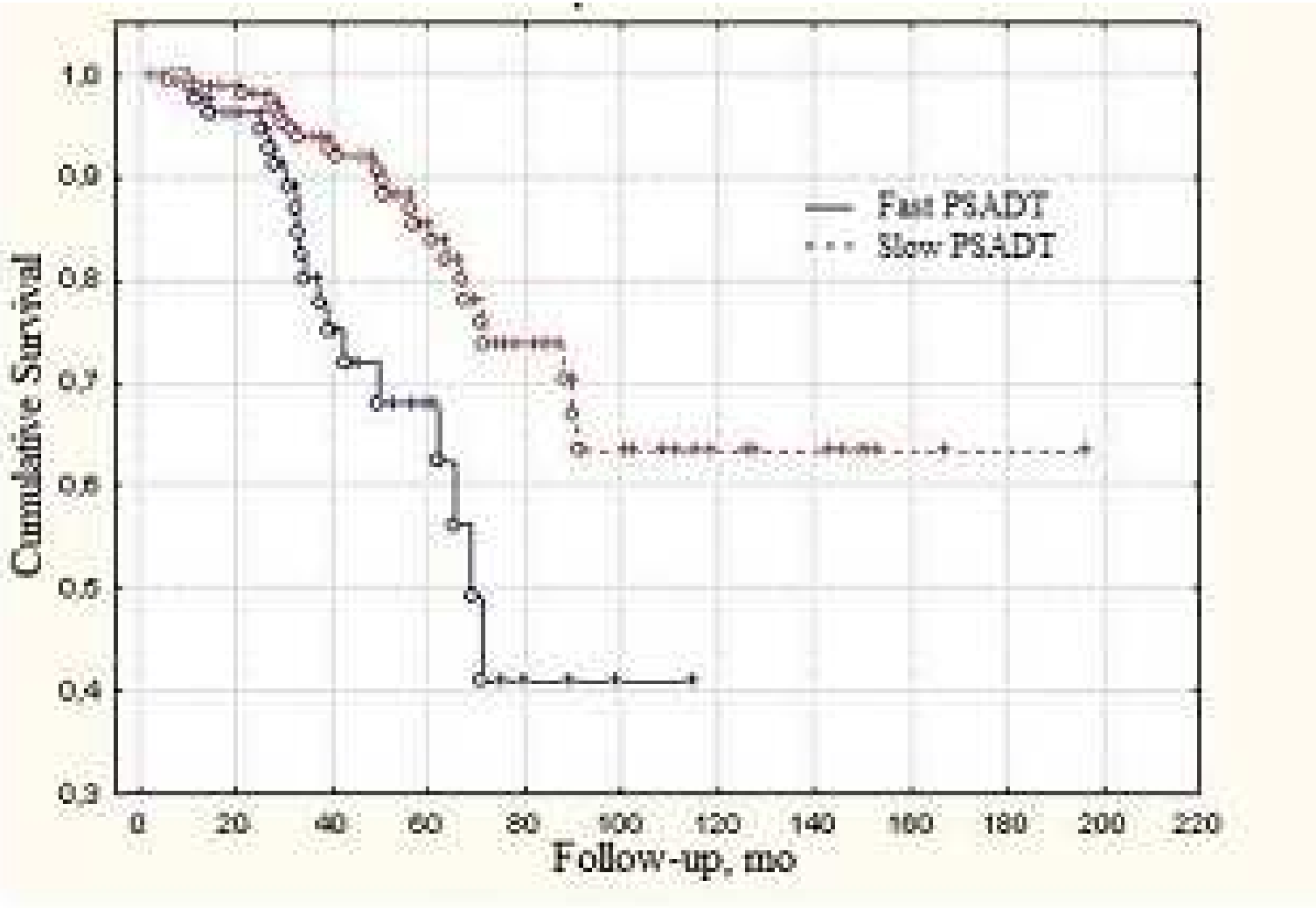


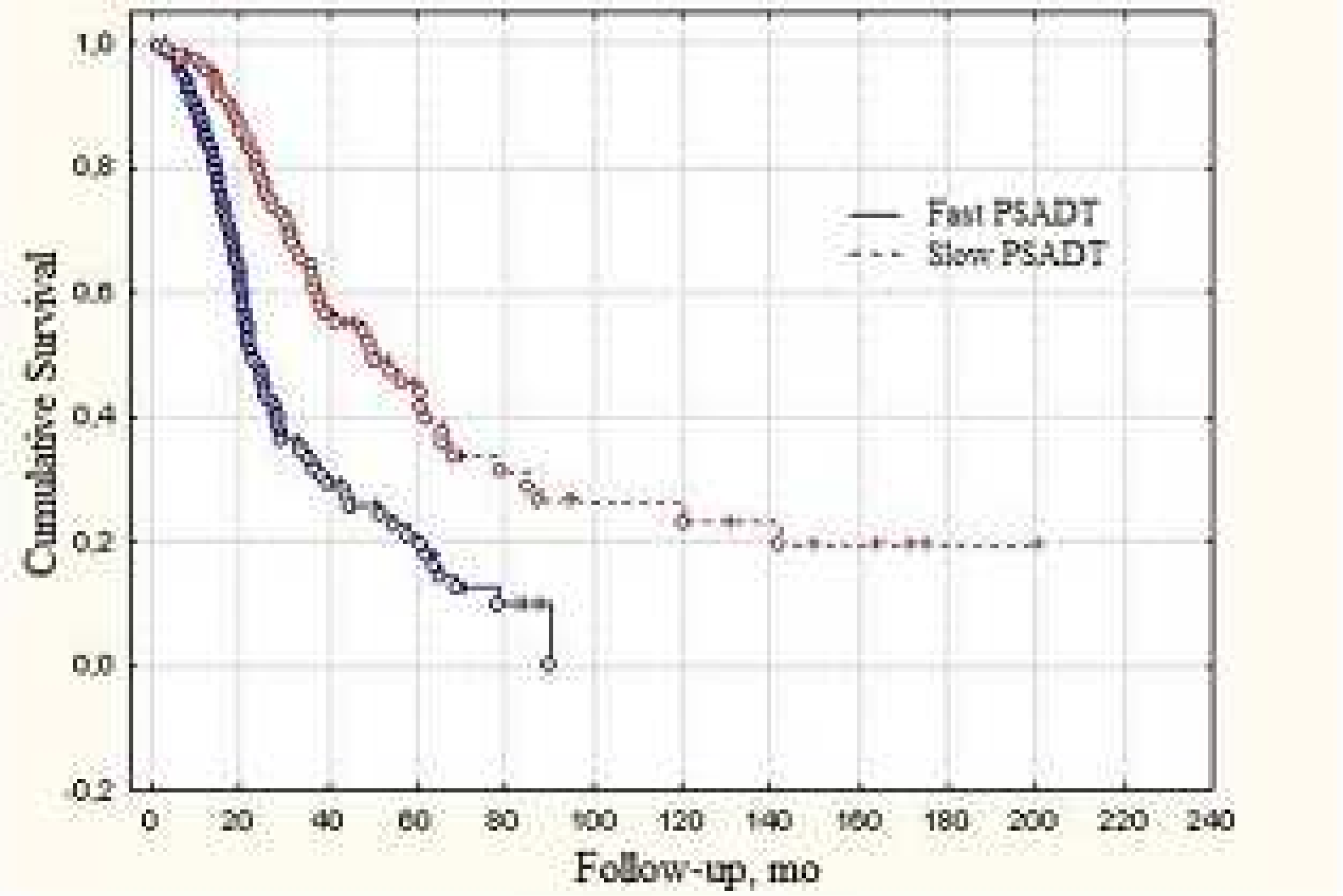
Figure 1: Total survival of local prostate cancer patients depending on PSADT.

Locally Advanced



gure 2: Total survival of local-advanced prostate cancer patients depending on PSADT.

Metastatic



ure 3: Total survival of generalized (metastatic) prostate cancer patients depending on PSADT.

PSA doubling time (PSADT) as Prognostic factor

Table 1: The PSA-doubling time in patients with different rate of prostate cancer dissemination

Parameters	Number of patients	%	Median PSADT, months (IQR)	*p**
Dissemination:				
Local	360	39.4	24.5 (8.0 – 69.7)	
Local-advanced	276	30.3	12.2 (4.3 – 36.6)	
Metastatic	276	30.3	2.4 (1.1 – 7.1)	
Gleason's index:				< 0.00001
< 6	265	36.4	20.8 (7.4 – 63.4)	
7	242	33.2	9.0 (3.0 – 27.3)	
8-10	222	30.5	3.9 (1.3 – 15.4)	
Primary PSA level, ng/ml				
< 10.0	193	21.2	36.3 (14.4 – 98.1)	
10.1-30.0	357	39.1	13.2 (4.9 – 39.4)	
30.1-100.0	323	25.4	4.5 (1.9 – 17.5)	
> 100.1	130	14.3	1.5 (0.8 – 4.6)	

T Staging

Primary Tumor (T)

Clinical

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Clinically inapparent tumor neither palpable nor visible by imaging
T1a	Tumor incidental histologic finding in 5% or less of tissue resected
T1b	Tumor incidental histologic finding in more than 5% of tissue resected
T1c	Tumor identified by needle biopsy (e.g., because of elevated PSA)
T2	Tumor confined within prostate*
T2a	Tumor involves one-half of one lobe or less
T2b	Tumor involves more than one-half of one lobe but not both lobes
T2c	Tumor involves both lobes
T3	Tumor extends through the prostate capsule**
T3a	Extracapsular extension (unilateral or bilateral)
T3b	Tumor invades seminal vesicle(s)
T4	Tumor is fixed or invades adjacent structures other than seminal vesicles such as external sphincter, rectum, bladder, levator muscles, and/or pelvic wall (Figure 41.1)

Recurrence Risk for Clinically Localized Prostate Cancer

- **Low Risk:**
  - T1-T2a and Gleason score 2-6 and PSA < 10 ng/ml
- **Intermediate Risk:**
  - T2b-T2c or Gleason score 7 or PSA 10-20
- **High Risk:**
  - T3a or Gleason score 8-10 or PSA > 20
- **Very High Risk:**
  - T3b-T4(locally advanced)

Biological factors

- **E-cadherin**
  - **It is a cohesive protein present on epithelial cells**
  - **Responsible for cell to cell adhesion**
  - **Responsible to maintain the tissue architecture**

Low level is associated with poor survival

Biological factors

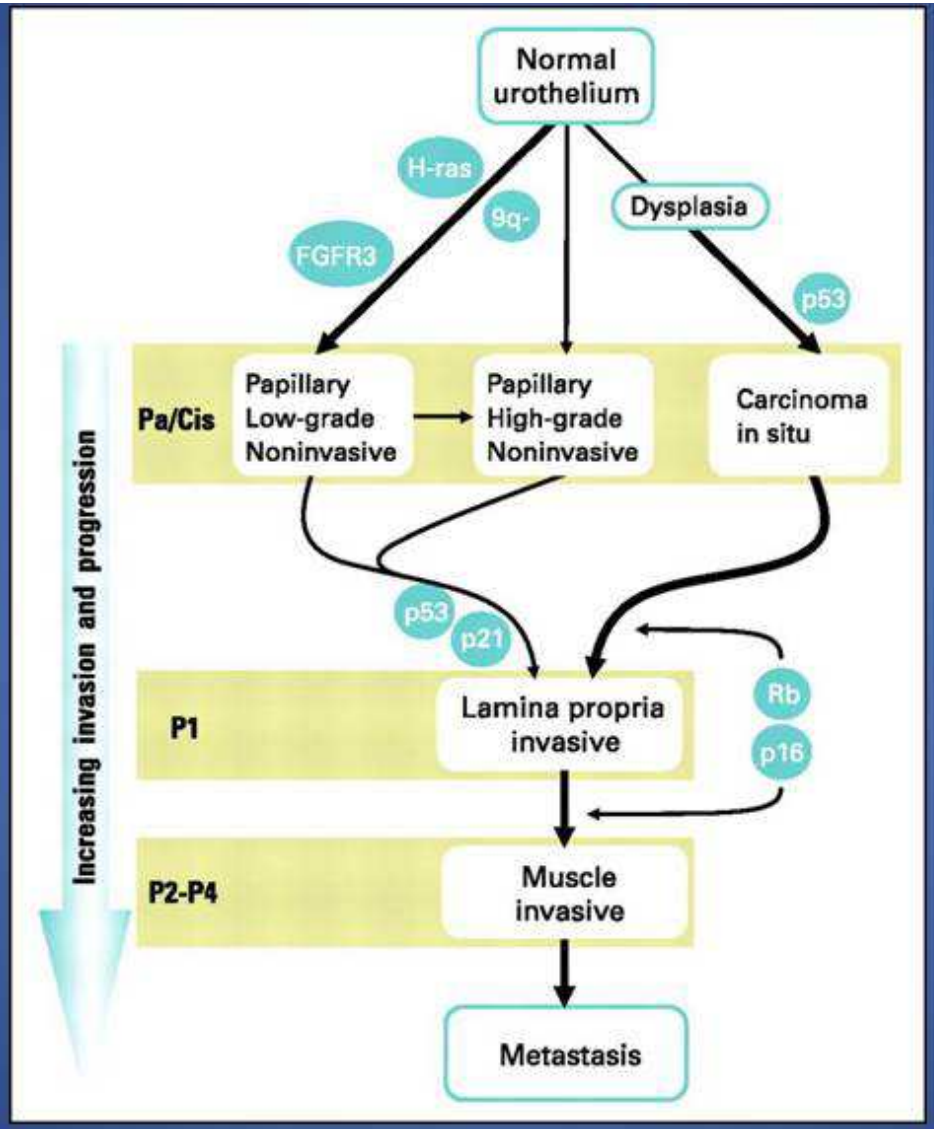
- **Microvessel density (MVD)**
  - *Higher MVD poor survival*
- **Androgen Receptor (AR)**
  - *High AR is associated with poor survival*
- **P53 abnormal Protein**
  - *Poor prognostic factor*
- **P27 Suppressor gene**
  - *Low level with poor survival*
- **DNA Ploidy**
  - *Diploid have better survival*

Proliferative Index

- **Ki-67**
  - ***Higher value is associated with poor survival***
- **S-phase fraction**
  - ***Higher value is associated with poor survival***

Urinary Bladder

Tumorigenesis & Progression



Mitra AP et al. J Clin Oncol 2006
Cote R, ASCO GU 2009

Superficial Bladder Tumour

- Number of Lesions
- Size
- T Stage (Ta or T1)
- CIS (Yes or No)
- Grade
- Prior Recurrence Rate

EORTC Scoring System

Factor	Recurrence	Progression
Number of tumours		
Single	0	0
2–7	3	3
≥8	6	3
Tumour diameter		
<3 cm	0	0
≥3 cm	3	3
Prior recurrence rate		
Primary tumour	0	0
≤1 recurrence/year	2	2
>1 recurrence/year	4	2
Category		
Ta	0	0
T1	1	4
CIS		
No	0	0
Yes	1	6
Grade		
G1	0	0
G2	1	0
G3	2	5
Total score	0–17	0–23

Sylvester RJ, van der Meijden APM, Oosterlinck W, et al. EORTC trials. Eur Urol 2006;49:466–77.

EORTC Scoring System

Recurrence score	Recurrence risk group	Probability of recurrence at 5 yr (95% CI)
0	Low risk	31% (24–37%)
1–4	Intermediate risk	46% (42–49%)
5–9		62% (58–65%)
10–17	High risk	78% (73–84%)

Sylvester RJ, van der Meijden APM, Oosterlinck W, et al. EORTC trials. Eur Urol 2006;49:466–77.

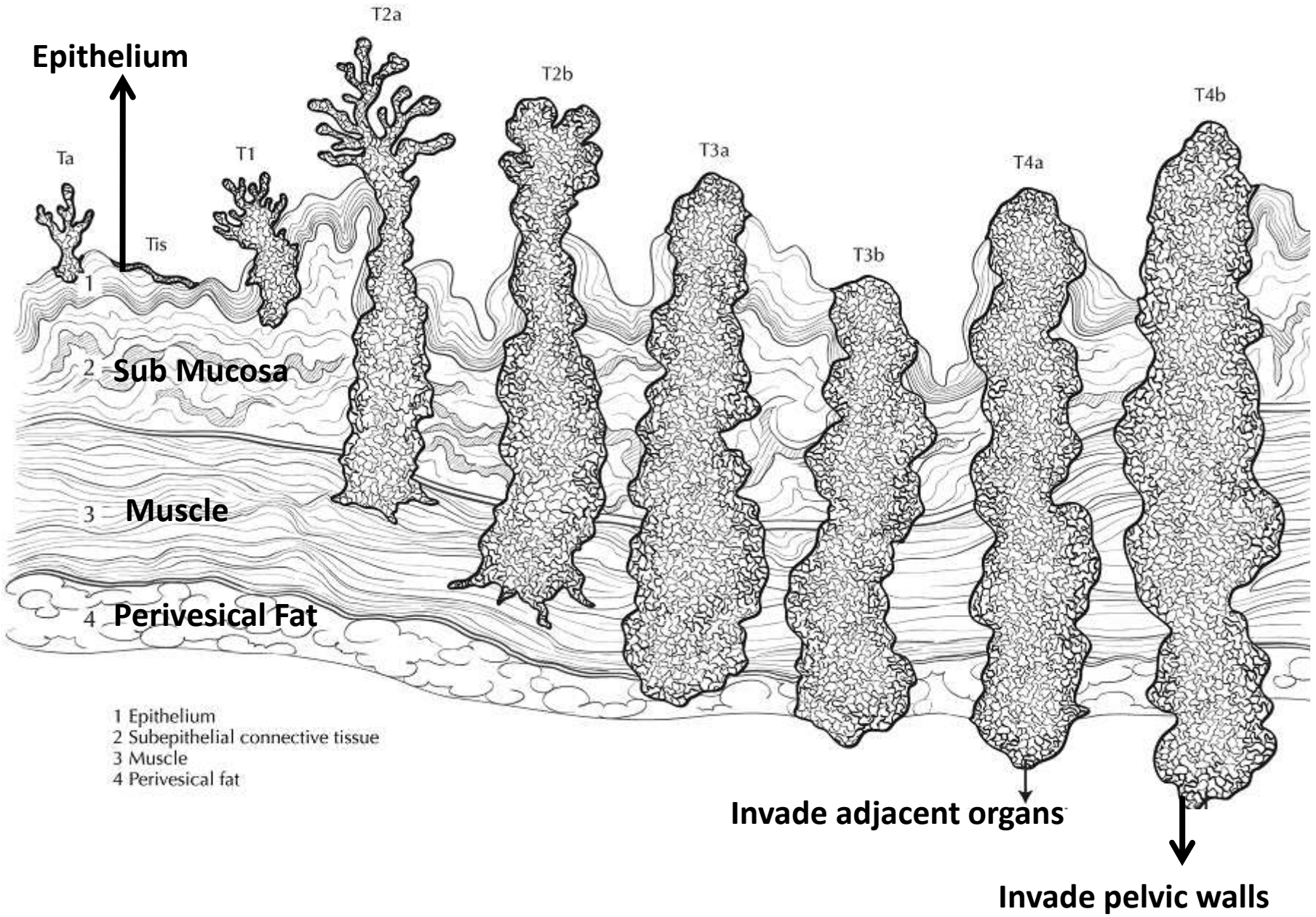
Prognostic Factors

- Age Older age is poor prognostic factor
- Gender Females do bad
- Size of the Primary 3cm or > 3 cm
- Positive Surgical margin Poor prognostic factor

Invasive Bladder Cancer

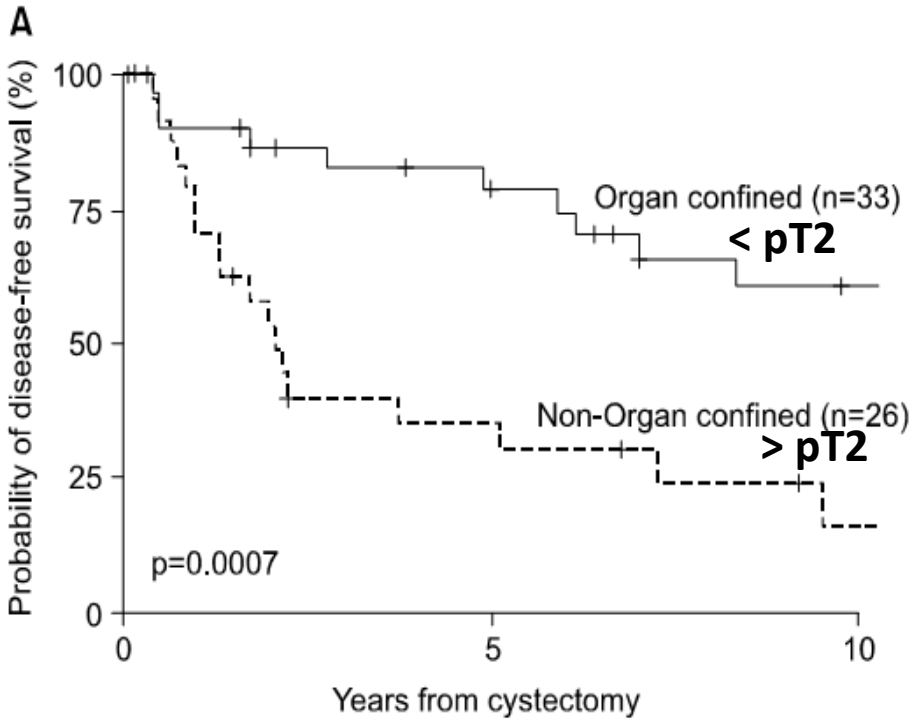
- T Stage
- Lymph nodes involvements
- LVI
- Performance Status
- Obstructive Uropathy
- Grade

TNM Staging

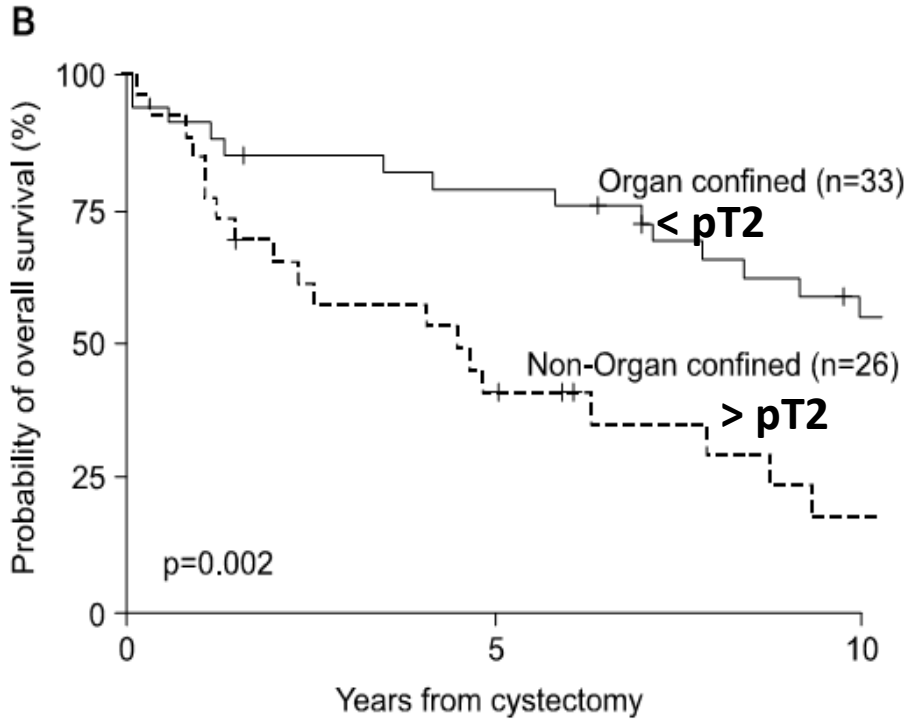

Epithelium
Ta
Tis
T1
T2a
T2b
T3a
T3b
T4a
T4b
1
2 Sub Mucosa
3 Muscle
4 Perivesical Fat
1 Epithelium
2 Subepithelial connective tissue
3 Muscle
4 Perivesical fat
Invade adjacent organs
Invade pelvic walls

T Stage

Disease Free Survival

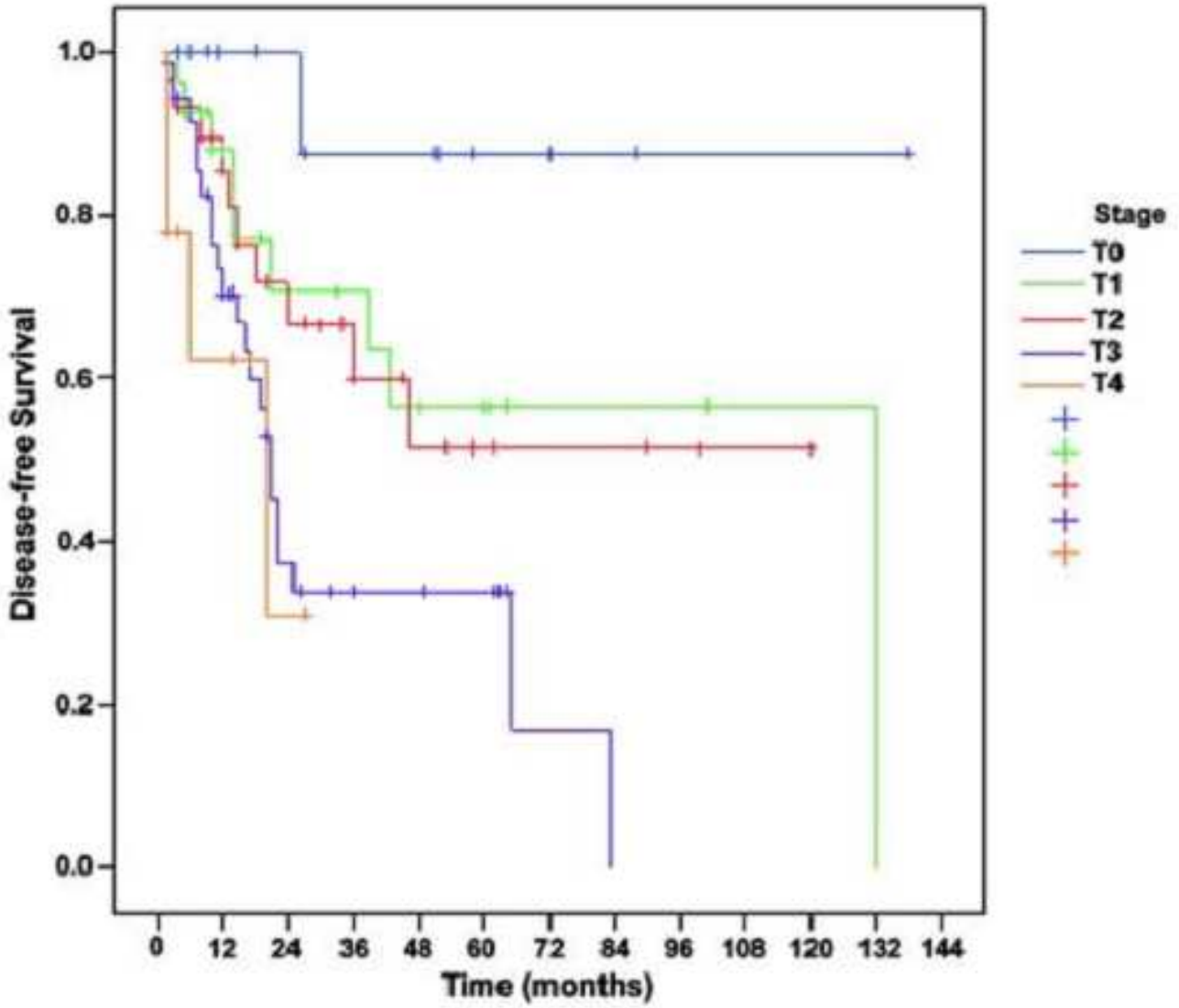


Over all Survival



Seung Hyun Jeon, et al : Long-term Follow-up of Radical Cystectomy for Bladder Cancer
Cancer Research and Treatment 2005;37(1)

T Stage



International Braz J Urol Vol. 32 (1): 35-42, January - February, 2006

T Stage

Outcomes after Radical Surgery in contemporary series -1

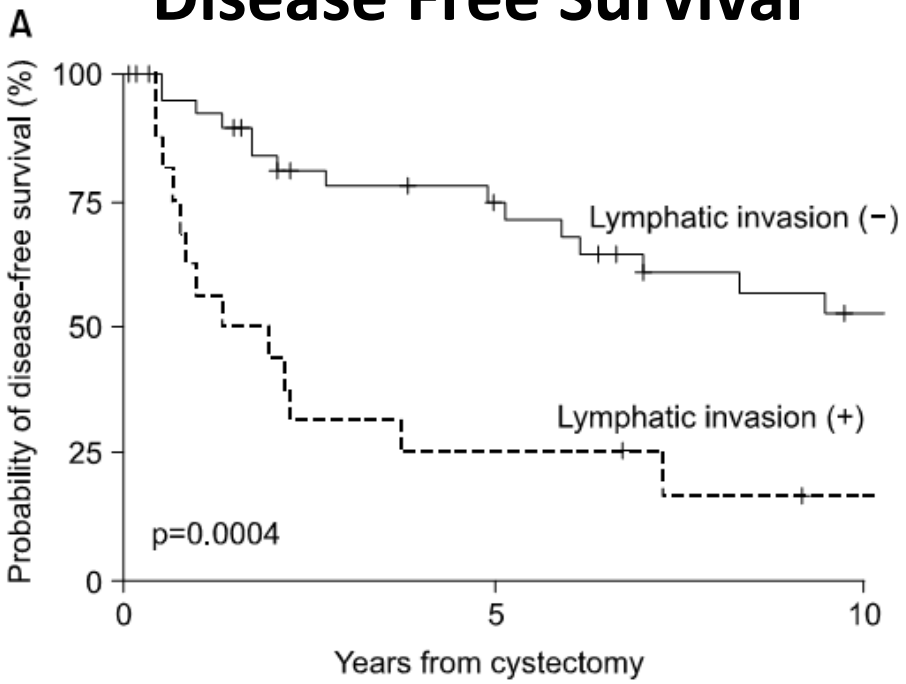
					5-yrs Survival (%)		
Series	Year	No.Pts	pT0-rate	Operative mortality	pT2	pT3	pT4
Roehrborn	1991	280	--	2.1	63	36	24
Pagano	1991	261	9	1.8	57	15	21
Wishnow	1992	188	5	1.1	79	46	33
Waehre	1993	227	25	--	61	36	29
Vieweg	1999	686	--	--	58	22	15
Stein	2001	633	6	3	72	48	33
Dalbagni	2001	284	10.7	--	59	25	29
Studer	2003	507	--	4.5	74	52	36
Grossman	2003	154	15	0.6	75	--	24
				Average:	**66%**	**35%**	**27%**

5-yrs OS for pT0 (95% CI): **83.5% (78.1-87.7)**

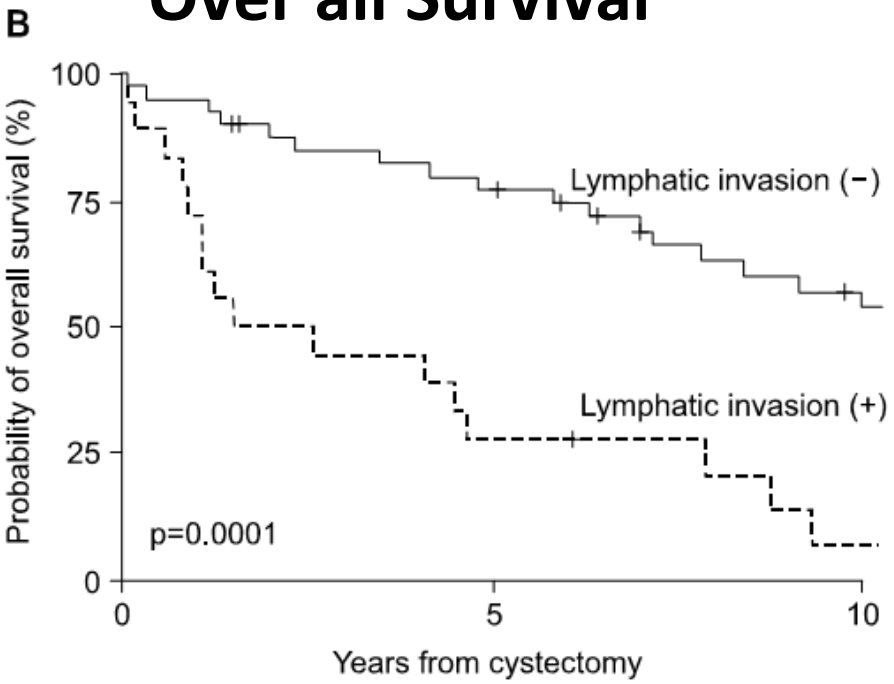
Herr HW, J Urol 2007 and Jacobs BL, CA Cancer J Clin 2010, Tilki D, J Urol 2010

Lymph node metastasis

Disease Free Survival



Over all Survival



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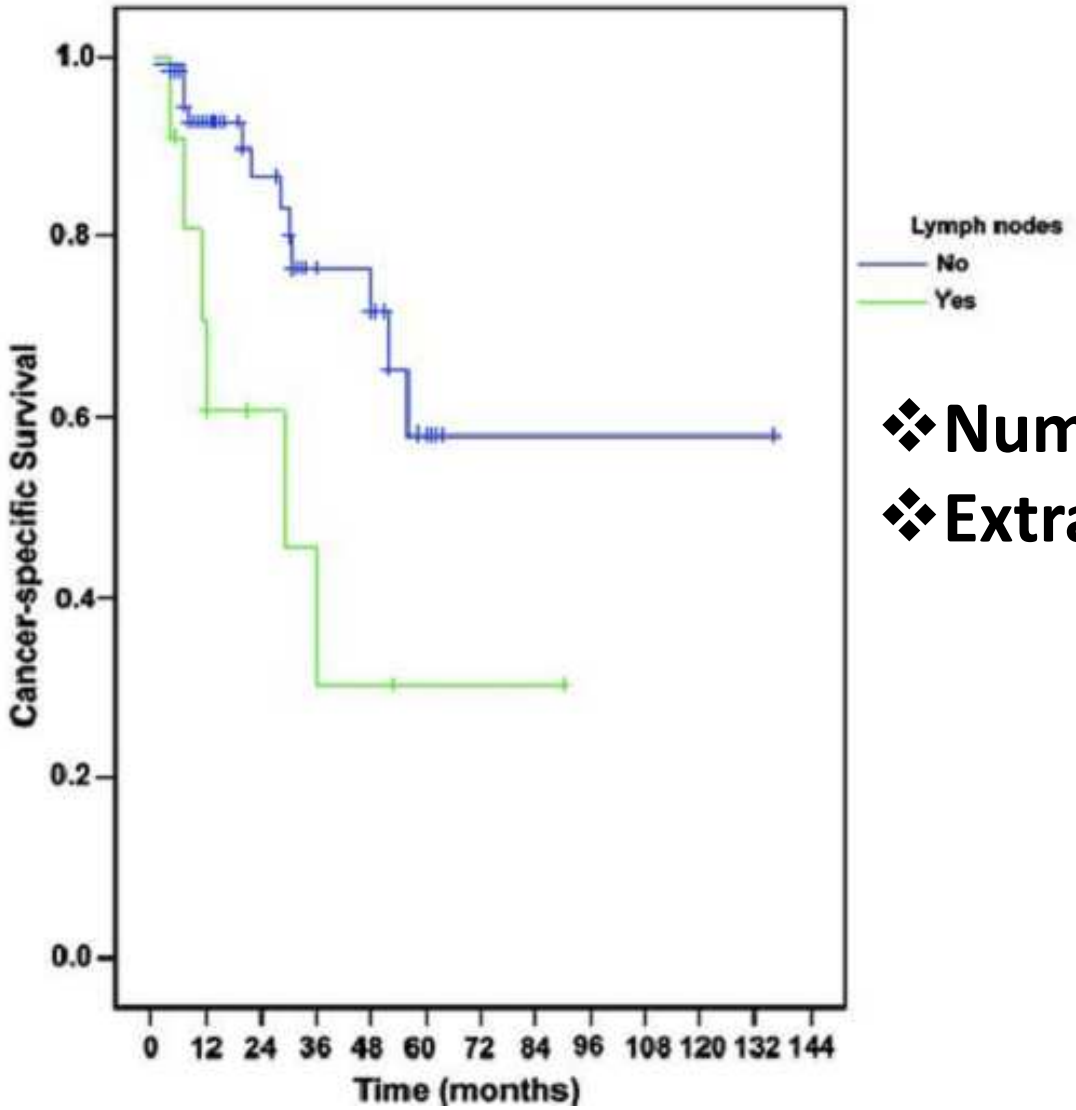
Lymph node metastasis



- ❖Number of nodal metastasis
- ❖Extra nodal extension

International Braz J Urol Vol. 32 (1): 35-42, January - February, 2006

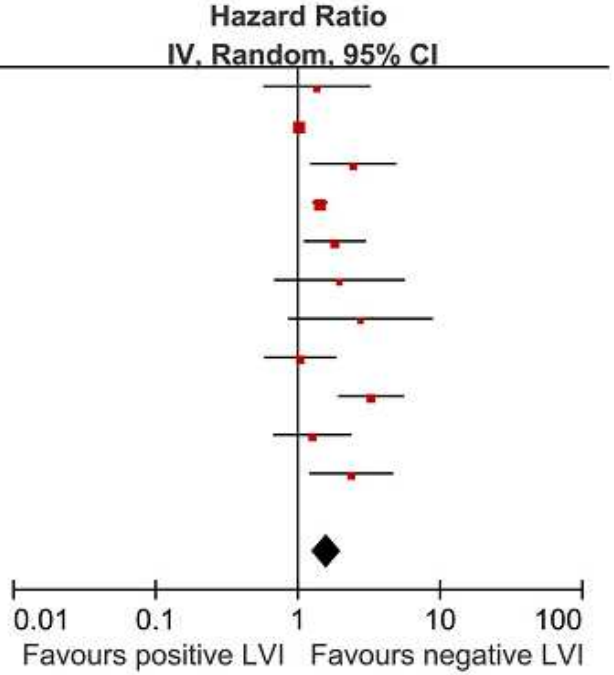
LVI

A. Recurrence Free Survival

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI	Year
Matsumoto	0.3075	0.4437	5.5%	1.36 [0.57, 3.25]	2008
Canter	0.0198	0.0099	17.8%	1.02 [1.00, 1.04]	2008
Streeper	0.8961	0.3557	7.3%	2.45 [1.22, 4.92]	2009
Shariat	0.3556	0.0619	17.1%	1.43 [1.26, 1.61]	2010
Hugen	0.5988	0.2569	10.2%	1.82 [1.10, 3.01]	2010
Kauffman	0.6729	0.5401	4.1%	1.96 [0.68, 5.65]	2011
Park(a)	1.0145	0.5981	3.5%	2.76 [0.85, 8.91]	2011
Park(b) (N+)	0.0383	0.2966	8.9%	1.04 [0.58, 1.86]	2011
Park(b) (N-)	1.183	0.2721	9.7%	3.26 [1.91, 5.56]	2011
Afonso	0.2359	0.3239	8.2%	1.27 [0.67, 2.39]	2013
Lotan	0.8629	0.3472	7.5%	2.37 [1.20, 4.68]	2013
Total (95% CI)			**100.0%**	**1.61 [1.26, 2.06]**	

Heterogeneity: $Tau^2 = 0.09$; $Chi^2 = 68.12$, df = 10 ($P < 0.00001$); $I^2 = 85\%$

Test for overall effect: $Z = 3.78$ ($P = 0.0002$)



Meta-Analysis of LVI in Invasive Bladder Cancer

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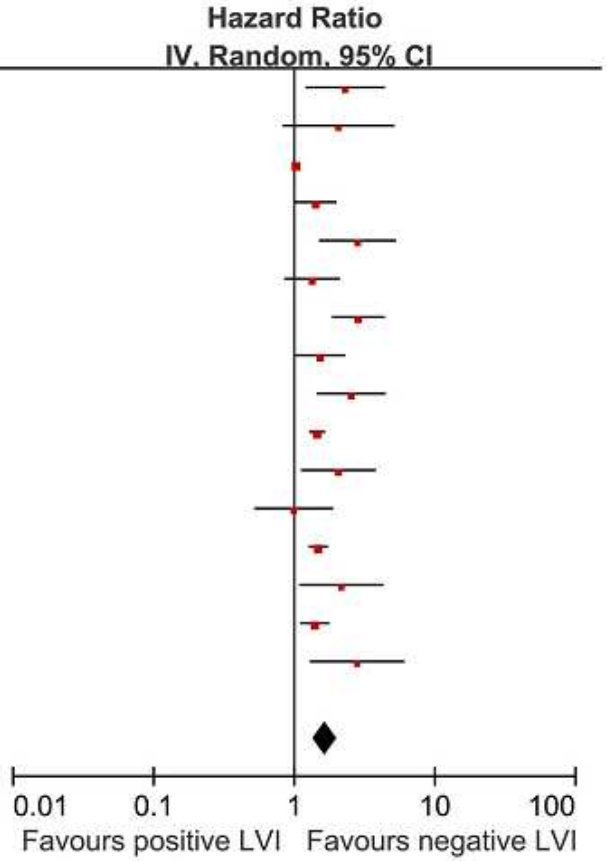
LVI

B. Cancer Specific Survival

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI	Year
Turkolmez	0.8329	0.3319	4.6%	2.30 [1.20, 4.41]	2007
Matsumoto	0.7227	0.47	2.9%	2.06 [0.82, 5.18]	2008
Canter	0.0296	0.01	10.1%	1.03 [1.01, 1.05]	2008
Fairey	0.3507	0.1738	7.6%	1.42 [1.01, 2.00]	2009
Streeper	1.0367	0.3221	4.7%	2.82 [1.50, 5.30]	2009
Manoharan	0.2927	0.2322	6.3%	1.34 [0.85, 2.11]	2010
Palmieri	1.0473	0.2205	6.6%	2.85 [1.85, 4.39]	2010
Kim	0.4253	0.2104	6.8%	1.53 [1.01, 2.31]	2010
Ku	0.9341	0.287	5.3%	2.54 [1.45, 4.47]	2010
Shariat	0.3736	0.0679	9.6%	1.45 [1.27, 1.66]	2010
Park(b) (N-)	0.7227	0.3123	4.9%	2.06 [1.12, 3.80]	2011
Park(b) (N+)	-0.008	0.3295	4.6%	0.99 [0.52, 1.89]	2011
Otto	0.392	0.0821	9.4%	1.48 [1.26, 1.74]	2012
Gondo	0.771	0.3513	4.3%	2.16 [1.09, 4.30]	2012
Eisenberg	0.3365	0.123	8.7%	1.40 [1.10, 1.78]	2013
Lotan	1.0296	0.3954	3.7%	2.80 [1.29, 6.08]	2013
Total (95% CI)			**100.0%**	**1.67 [1.38, 2.01]**	

Heterogeneity: $Tau^2 = 0.09$; $Chi^2 = 118.81$, df = 15 ($P < 0.00001$); $I^2 = 87\%$

Test for overall effect: $Z = 5.35$ ($P < 0.00001$)



Meta-Analysis of LVI in Invasive Bladder Cancer

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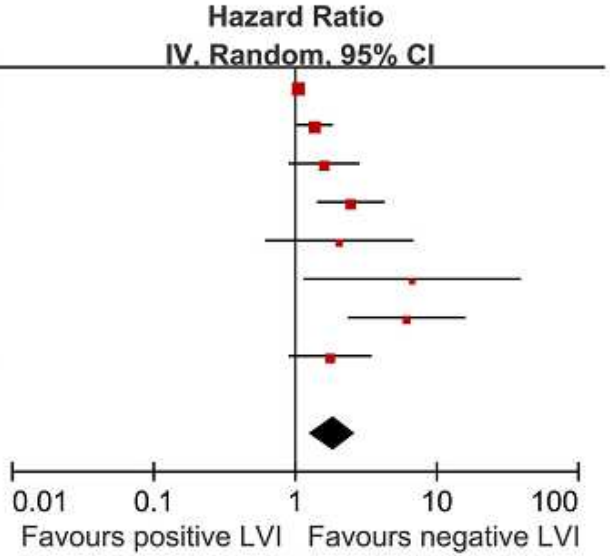
LVI

C. Over all Survival

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI	Year
Canter	0.0488	0.0098	21.4%	1.05 [1.03, 1.07]	2008
Fairey	0.3148	0.1505	18.8%	1.37 [1.02, 1.84]	2009
Stephenson	0.47	0.2936	14.1%	1.60 [0.90, 2.84]	2010
Ku	0.9014	0.281	14.5%	2.46 [1.42, 4.27]	2010
Kauffman	0.7129	0.616	6.5%	2.04 [0.61, 6.82]	2011
Park(a)	1.9012	0.9018	3.6%	6.69 [1.14, 39.20]	2011
Font	1.8116	0.4883	8.8%	6.12 [2.35, 15.94]	2011
Afonso	0.567	0.3442	12.5%	1.76 [0.90, 3.46]	2013
Total (95% CI)			**100.0%**	**1.84 [1.27, 2.66]**	

Heterogeneity: $Tau^2 = 0.17$; $Chi^2 = 34.89$, df = 7 ($P < 0.0001$); $I^2 = 80\%$

Test for overall effect: $Z = 3.25$ ($P = 0.001$)

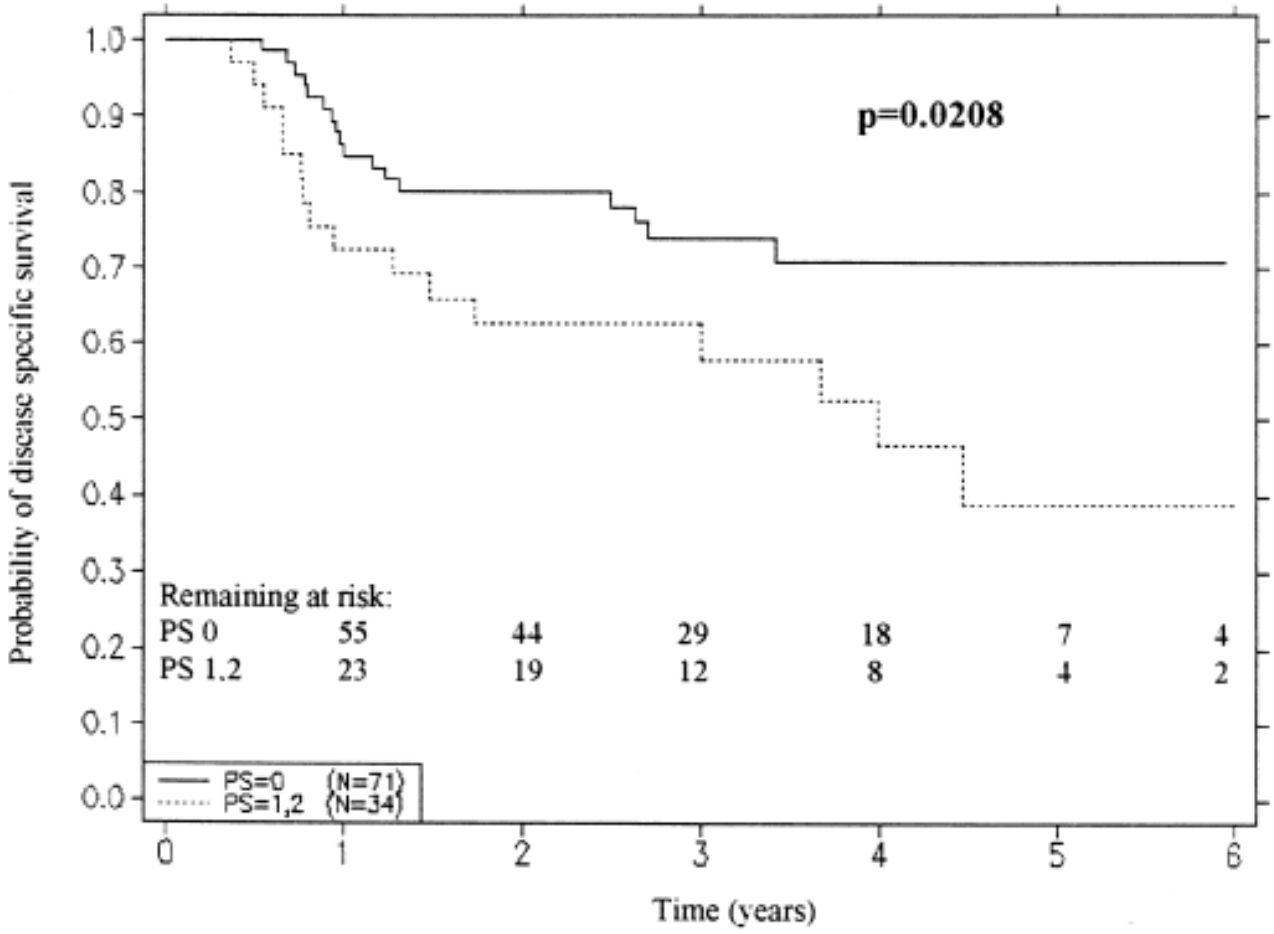


Meta-Analysis of LVI in Invasive Bladder Cancer

February 2014 | Volume 9 | Issue 2 | e89259

Performance Status

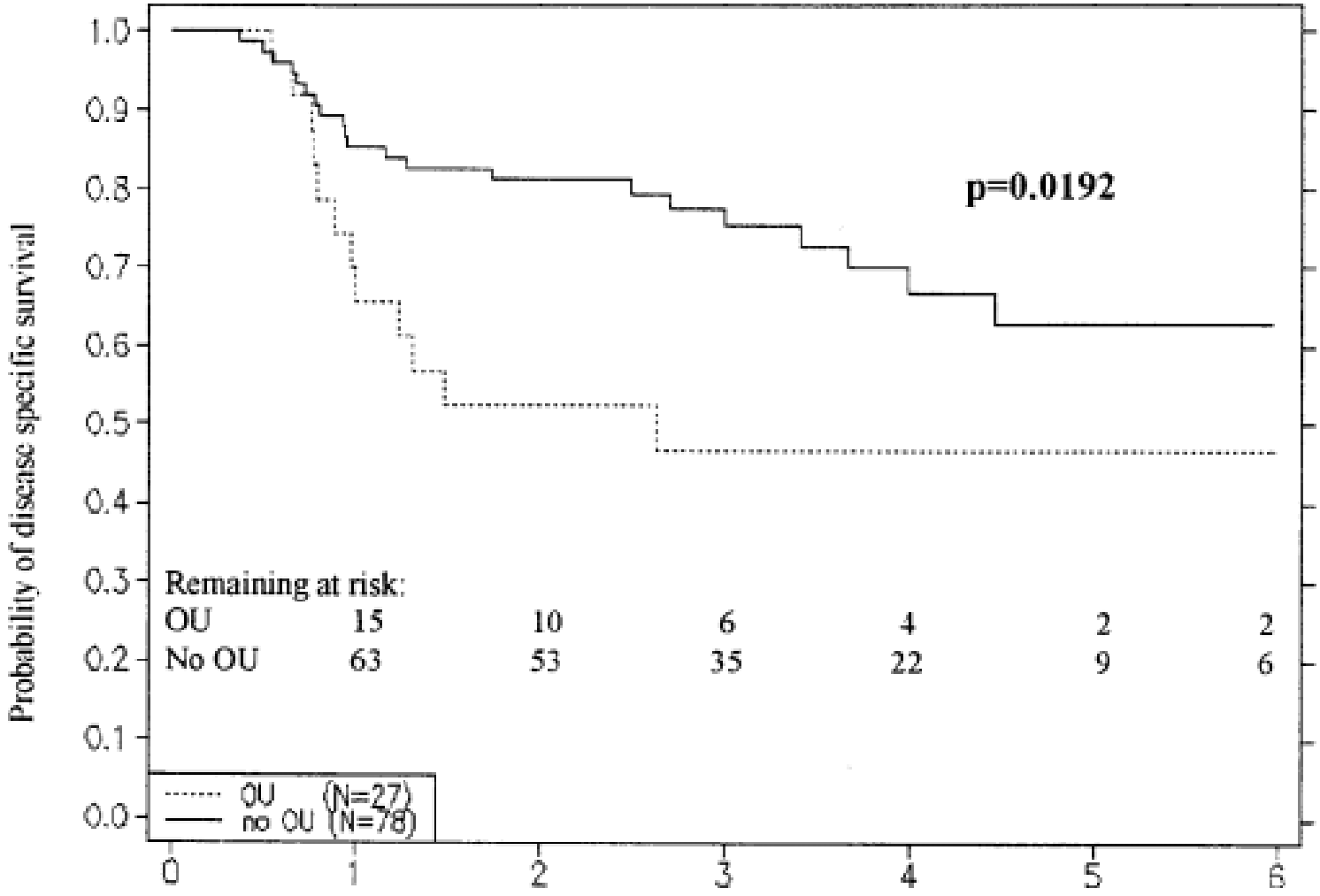
Specially for patients treated by Bladder Preservation Treatment



I. J. Radiation Oncology ● Biology ● Physics Volume 46, Number 2, 2000

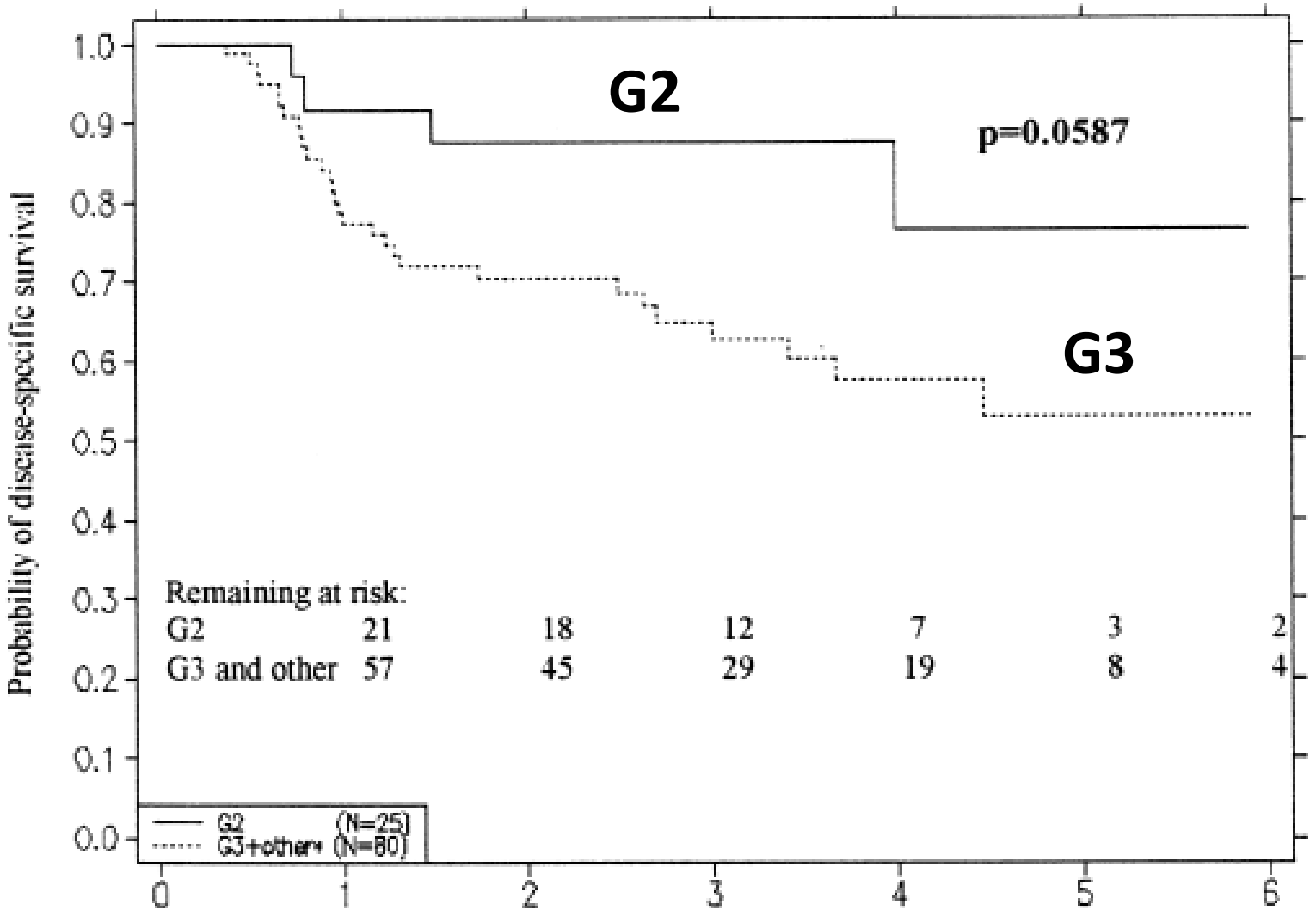
Presence of Obstructive Uropathy

Specially for patients treated by Bladder Preservation Treatment



I. J. Radiation Oncology ● Biology ● Physics Volume 46, Number 2, 2000

Grade of the Tumour

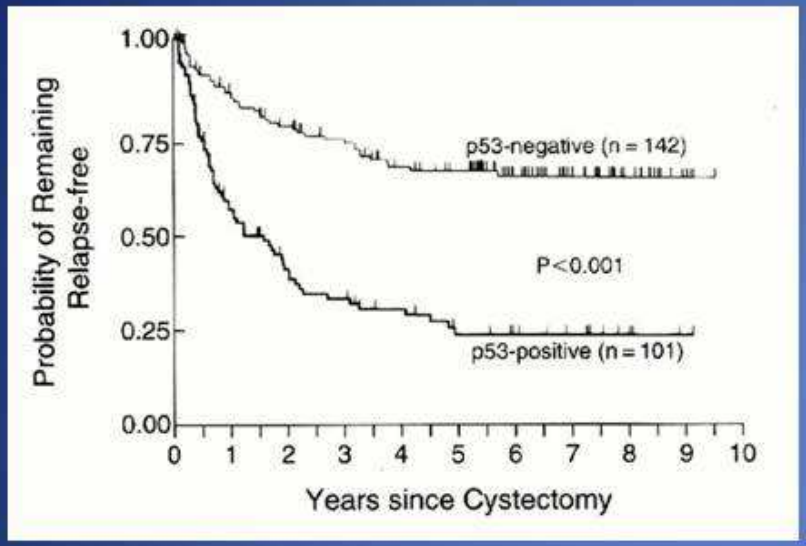


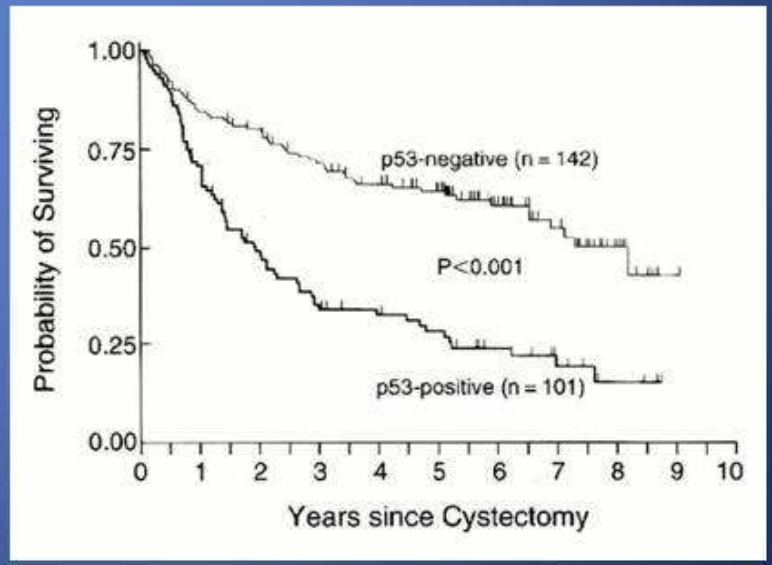
I. J. Radiation Oncology ● Biology ● Physics Volume 46, Number 2, 2000

Biomarkers

p53

Probability of remaining recurrence-free in bladder cancer with respect to p53 IHC status

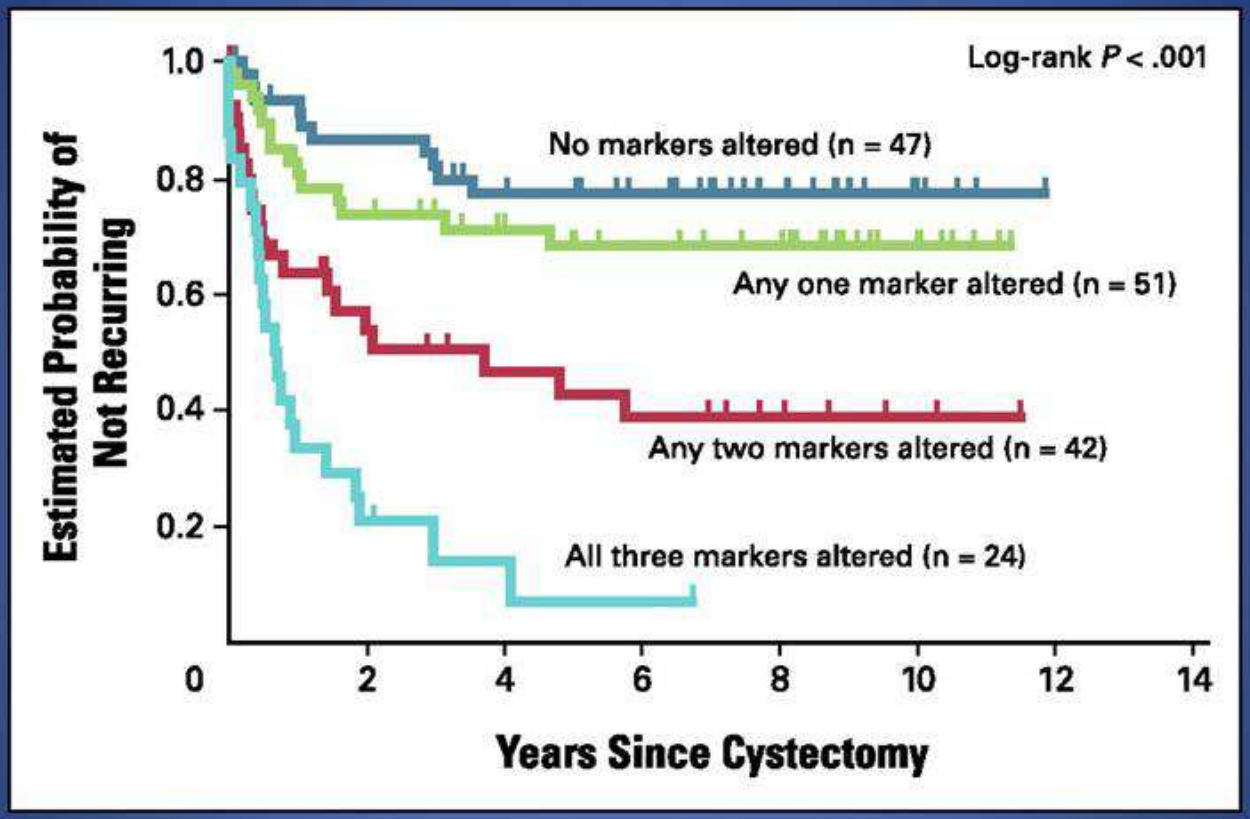




Esrig D et al. N Engl J Med 1994

P53/p21/Rb

p53/p21/Rb in Bladder cancer
Effect of coordinate molecular alterations

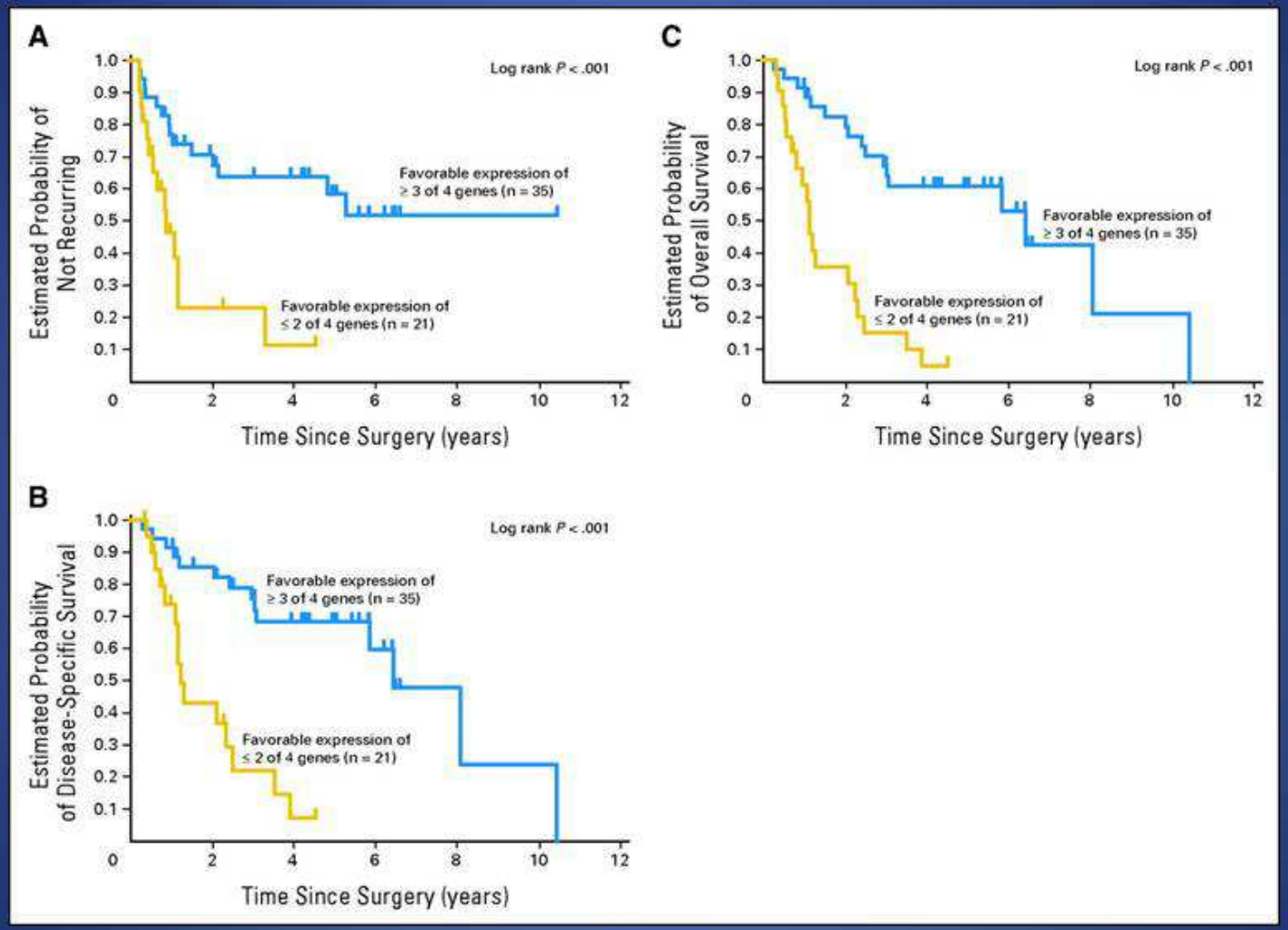


Probability of recurrence-free survival in 164 bladder cancer patients, who underwent radical cystectomy, based on alterations in **p53**, **p21**, and/or **Rb** expression (as detected by IHC)

Mitra AP, J Clin Oncol 2006
Chatterjee SJ, J Clin Oncol 2004

Gene Signatures

Generation of a predictive expression signature in urothelial carcinoma



Mitra AP, J Clin Oncol 2009

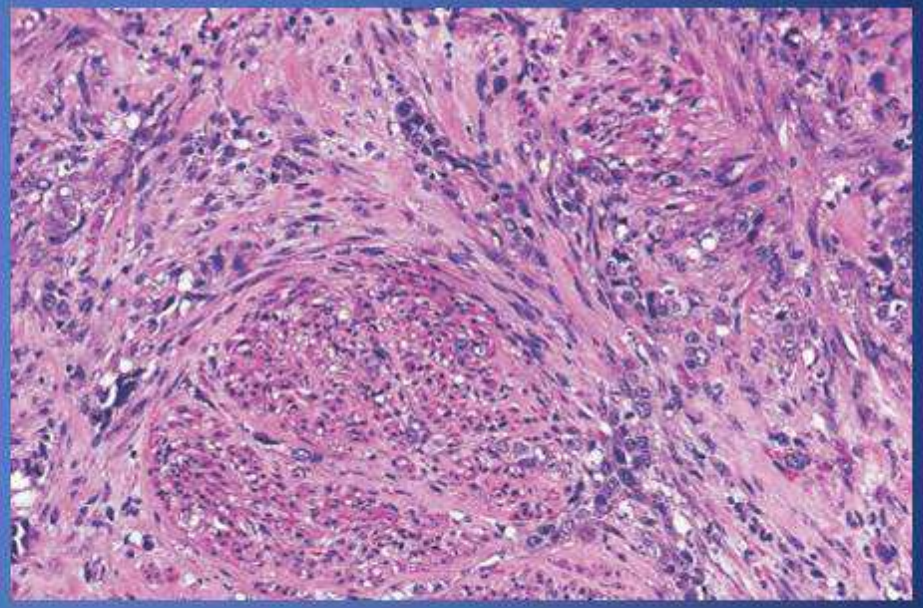
Over expression of growth factors

- **EGFR** is overexpressed in 31-48% high-grade muscle invasive disease
  (Lipponen P, Br J Cancer 1994, Villares JP, World J Urol 2007)

- **VEGF** and VEGFR2 are overexpressed and VEGFR2 correlates with tumor stage

- **HER2/neu:** only 5% of TCC patients eligible to anti-HER2 treatment
  Latif Z, Eur J Cancer 2001
  Laè M, Ann Oncol 2010

- **Human RAS** (HRAS): activating mutations have been recognized in 30-40% of TCCs, expecially superficial tumors.
  Dinney CP, Cancer Cell 2004



Testicular Cancers

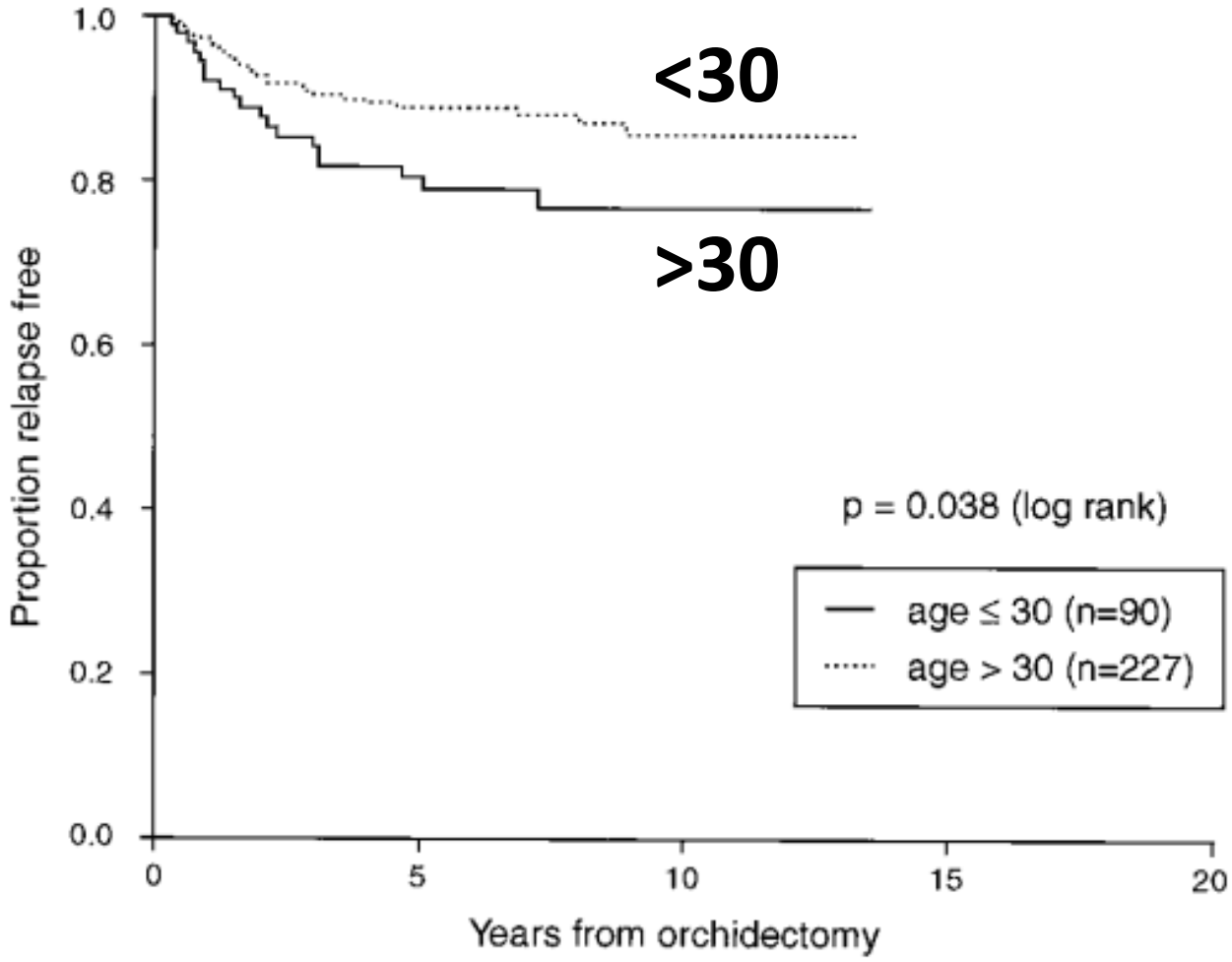
Management Decision in Stage I

Active Surveillance

Treatment

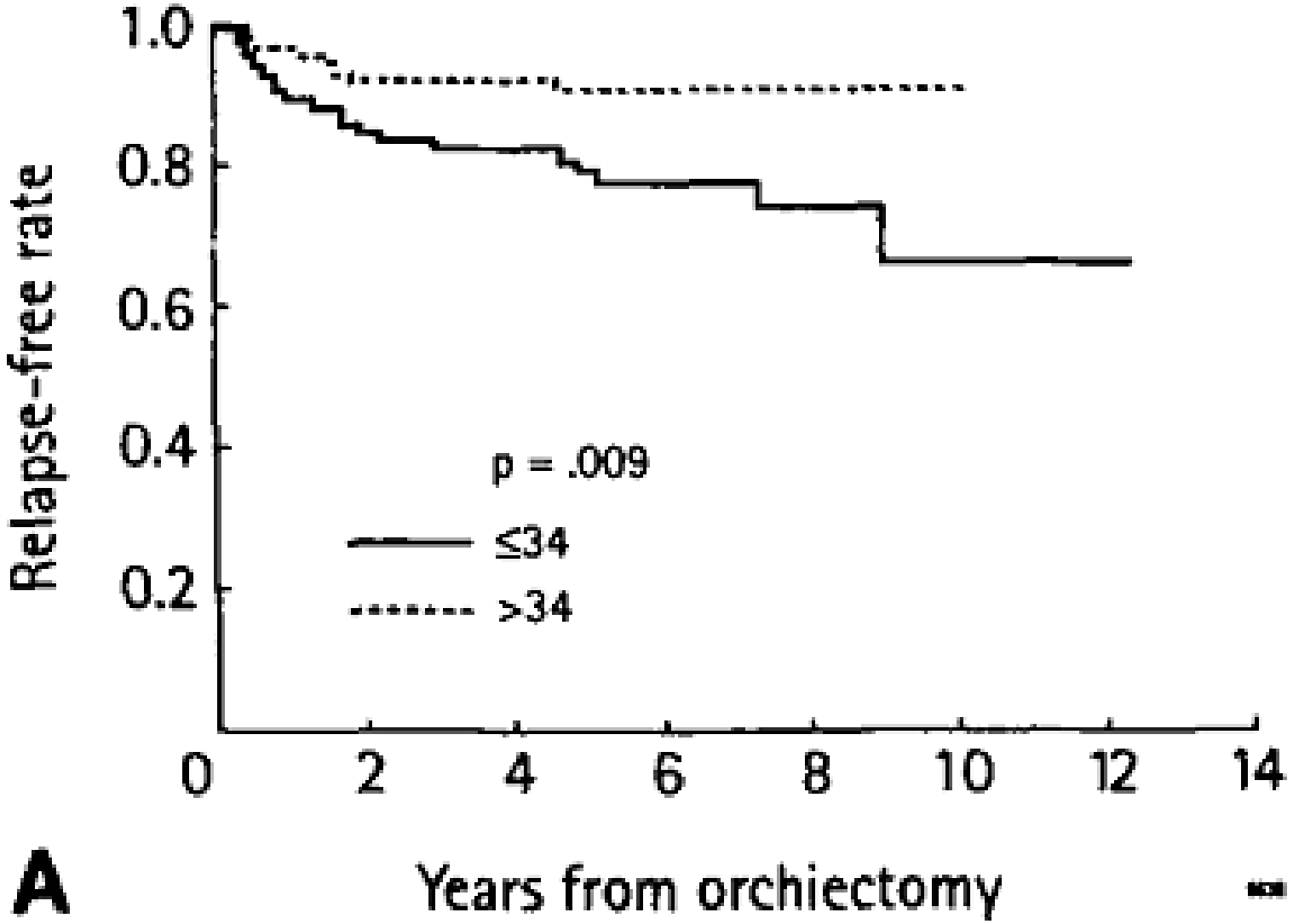
Age of the Patients

Specially applicable to Seminoma stage 1



Journal of Clinical Oncology, Vol 20, No 22 (November 15), 2002: pp 4448-4452

Age of the Patients

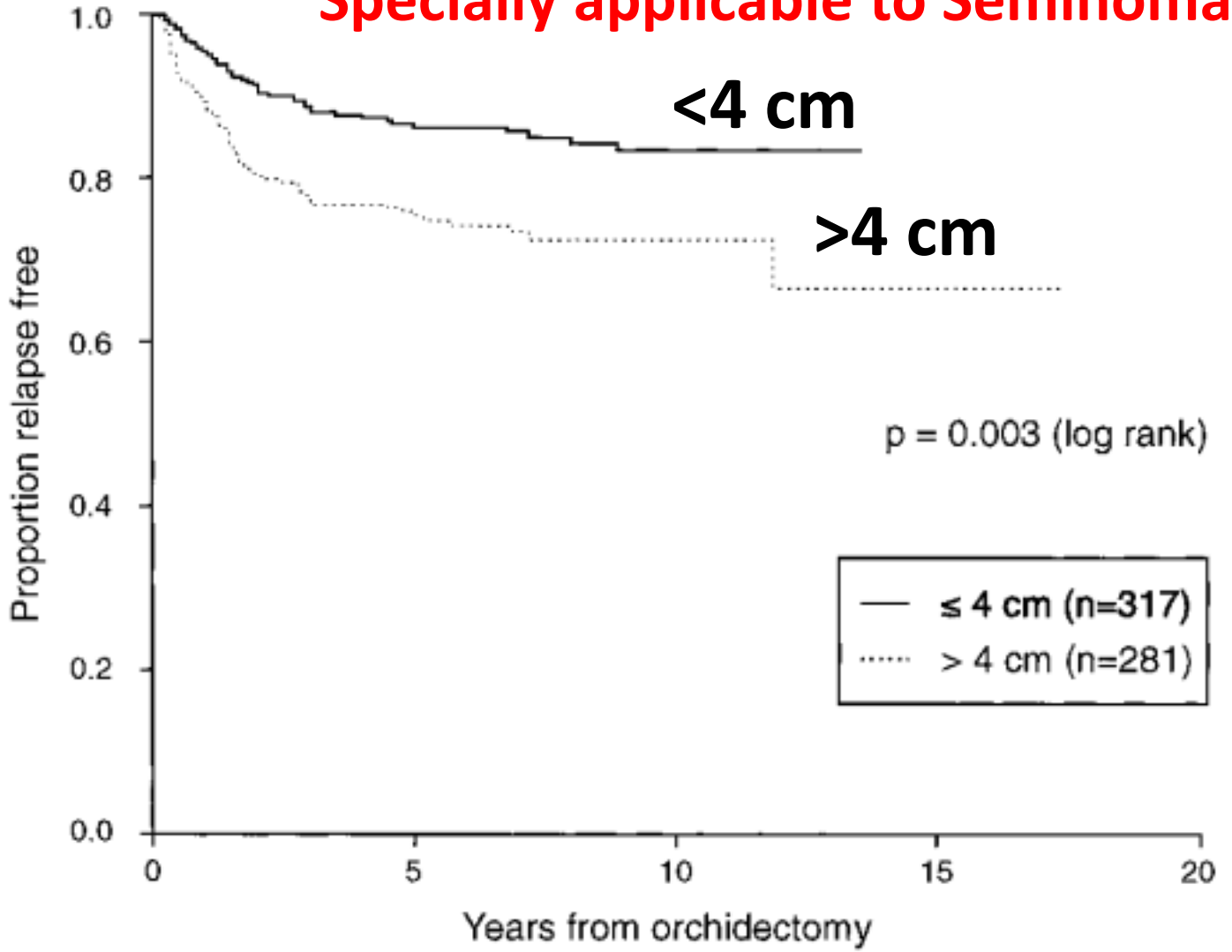


0022-5347/97/1575-1705$03.00/0
THE JOURNAL OF UROLOGY

Vol. 157, 1705–1710, May 1997
Printed in U.S.A.

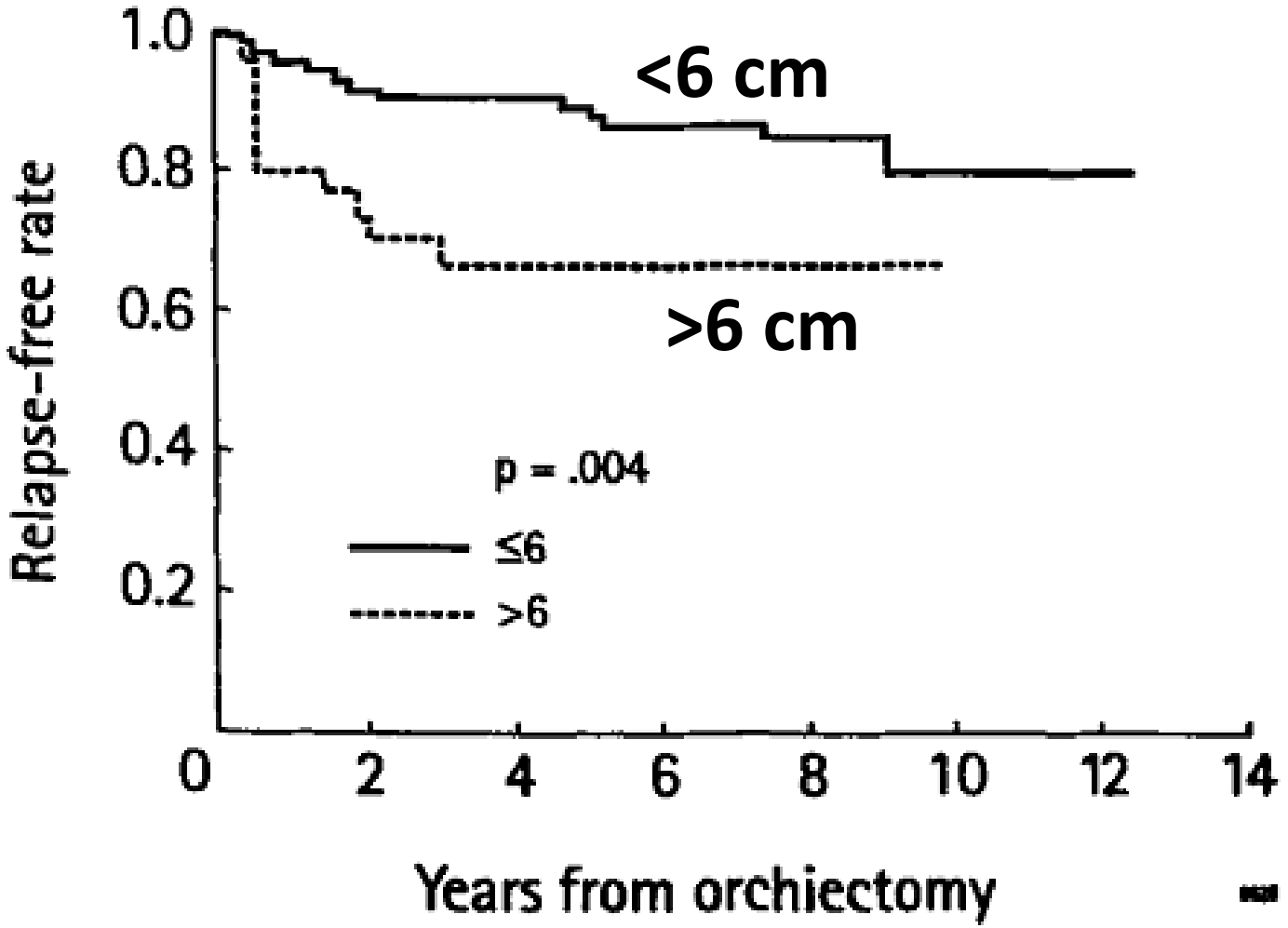
Size of the Tumour

Specially applicable to Seminoma stage 1



Journal of Clinical Oncology, Vol 20, No 22 (November 15), 2002: pp 4448-4452

Size of the Tumour

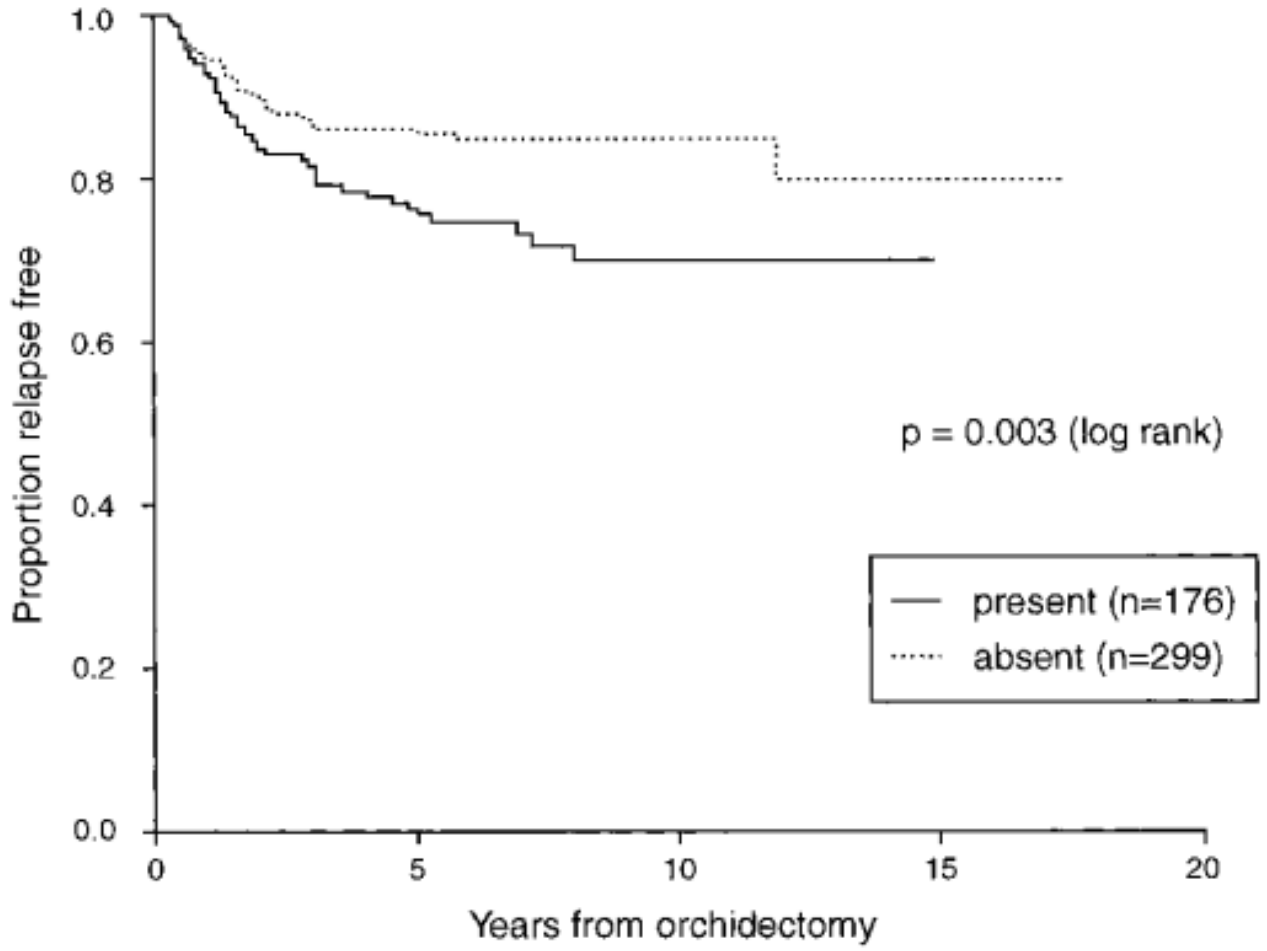


0022-5347/97/1575-1705$03.00/0
THE JOURNAL OF UROLOGY

Vol. 157, 1705–1710, May 1997
Printed in U.S.A.

Invasion of Rete Testis

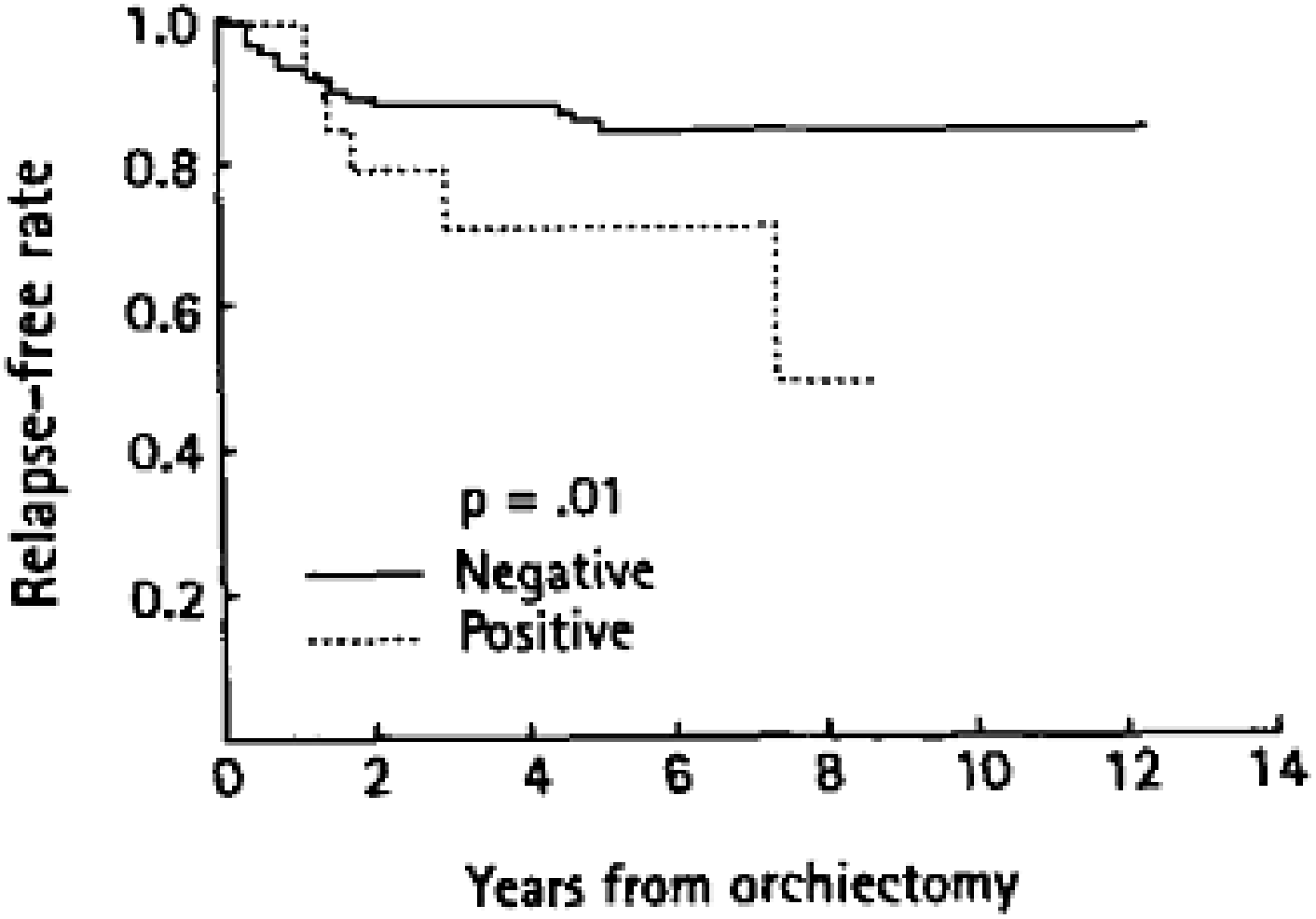
Specially applicable to Seminoma Stage 1



Journal of Clinical Oncology, Vol 20, No 22 (November 15), 2002: pp 4448-4452

Lympho Vascular Invasion

Specially applicable to Non-seminoma Stage 1



B

0022-5347/97/1575-1705$03.00/0
THE JOURNAL OF UROLOGY

Vol. 157, 1705–1710, May 1997
Printed in U.S.A.

Lympho Vascular Invasion

Specially applicable to Non-seminoma Stage 1

TABLE 2. Association of Histologic Characteristic With Occurrence of Metastasis

Histologic characteristic	With characteristics No.	With characteristics % Metastases	Without characteristics No.	Without characteristics % Metastases	P (X^2 Test)
Embryonal carcinoma	81	35	12	0	0.05
Endodermal sinus					
Seminoma	30	20	63	32	0.35
Vascular invasion	11	46	82	26	0.31
Lymphatic invasion	26	62	67	18	<0.01
Vascular and/or lymphatic invasion	32	53	61	18	<0.01

Embryonal Histology

STAGE I MIXED GERM CELL TUMORS · *Dunphy et al.* CANCER *September 15* 1988

Stage II and above (Seminoma)

- **Only site of metastasis is important**
  - Non-pulmonary visceral metastasis (eg. liver):
    - Absent: good prognostic group
    - Present: intermediate prognostic group
- Seminoma with metastasis in lymph nodes and lung is in good prognostic group
- **Seminoma never in poor prognostic group**

Stage II and above (Non-seminoma)

- **Prognostic grouping is based on**
  - Site of primary tumour
  - Site of metastasis
  - Serum marker levels
- Mediastinal primary or non-pulmonary visceral metastasis, or very high serum markers: poor prognosis group
- Otherwise good/intermediate based on serum marker levels

Serum Tumour Markers

- **Alphafeto Protein (AFP)**
- **Human Chorionic Gonadothropin (HCG)**
- **Lactase Dehydrogenase (LDH)**

Required for staging	Serum tumor markers (S)	
	SX	Marker studies not available or not performed
	S0	Marker study levels within normal limits
	S1	LDH < 1.5 × N* *and* hCG (mIu/ml) <5,000 *and* AFP (ng/ml) <1,000
	S2	LDH 1.5–10 × N *or* hCG (mIu/ml) 5,000–50,000 *or* AFP (ng/ml) 1,000–10,000
	S3	LDH > 10 × N *or* hCG (mIu/ml) > 50,000 *or* AFP (ng/ml) > 10,000

Advanced Tumours

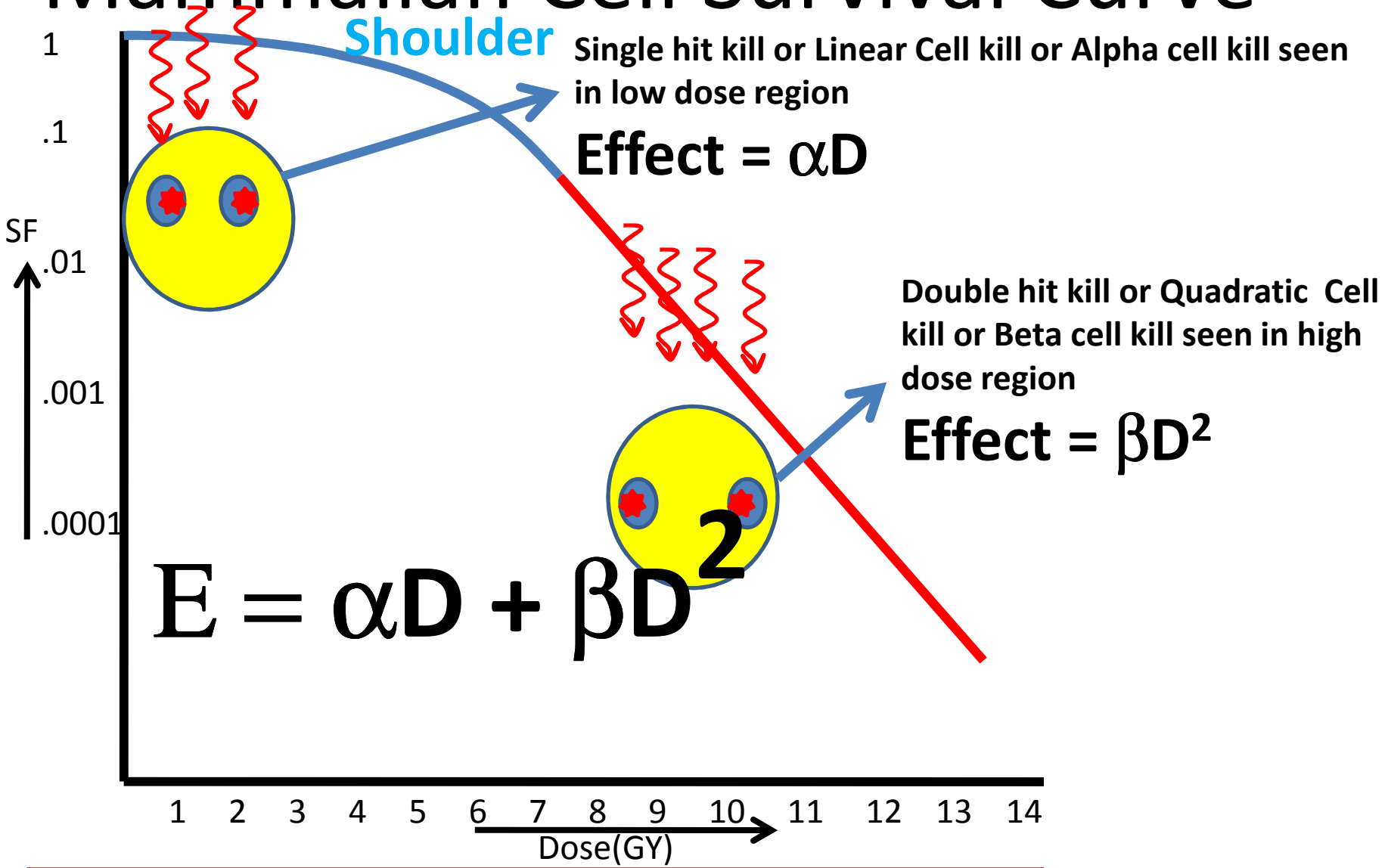
Risk Status	Nonseminoma	Seminoma
Good Risk	Testicular or retroperitoneal primary tumor and No nonpulmonary visceral metastasis and Post-orchiectomy markers all of: AFP < 1,000 ng/mL hCG < 5,000 iu/L LDH < 1.5 x upper limit of normal	Any primary site and No nonpulmonary visceral metastases and Normal AFP Any hCG Any LDH
Intermediate Risk	Testicular or retroperitoneal primary tumor and No nonpulmonary visceral metastasis And Post-orchiectomy markers any of: AFP 1,00 – 10,000 ng/mL hCG = 5,000 – 50,000 iu/L LDH = 1.5 – 10 x upper limit of normal	Any primary site and Nonpulmonary visceral metastases and Normal AFP Any hCG Any LDH
Poor Risk	Mediastinal primary tumor or Nonpulmonary visceral metastasis or Post-orchiectomy markers any of: AFP > 10,000 ng/mL hCG > 50,000 iu/L LDH > 10 x upper limit of normal	No poor risk classification for seminoma

Advanced Tumours

Prognostic Group	Tumour type	5 Year Progression Free Survival (%)	5 Year Survival (%)
Good	Seminoma (90%)	82	86
	Non-seminoma (56%)	89	92
Intermediate	Seminoma (10%)	67	72
	Non-seminoma (28%)	75	80
Poor	Seminoma (None)	-	-
	Non-seminoma (16%)	41	48

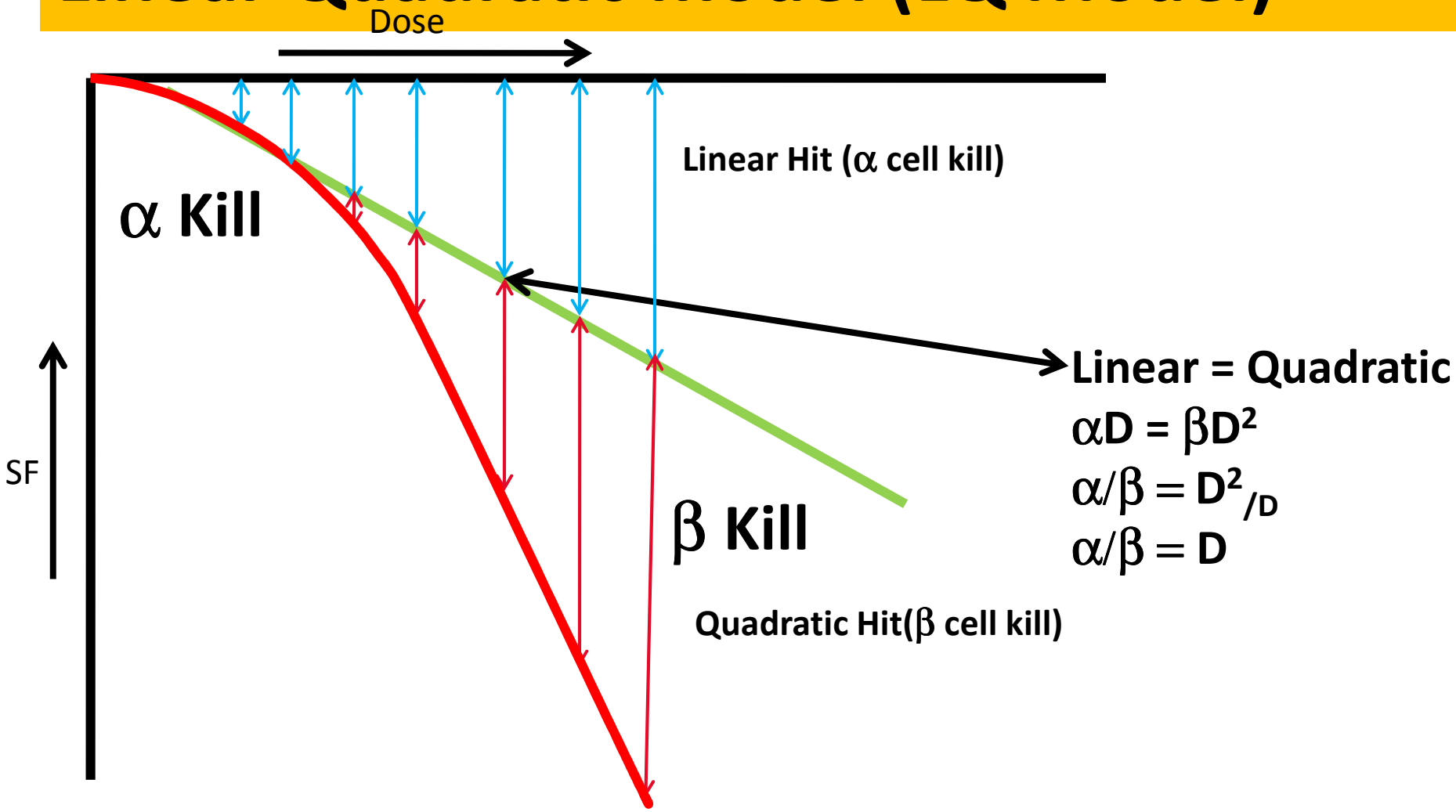
Radiobiology

Mammalian Cell Survival Curve



Linear-Quadratic Model

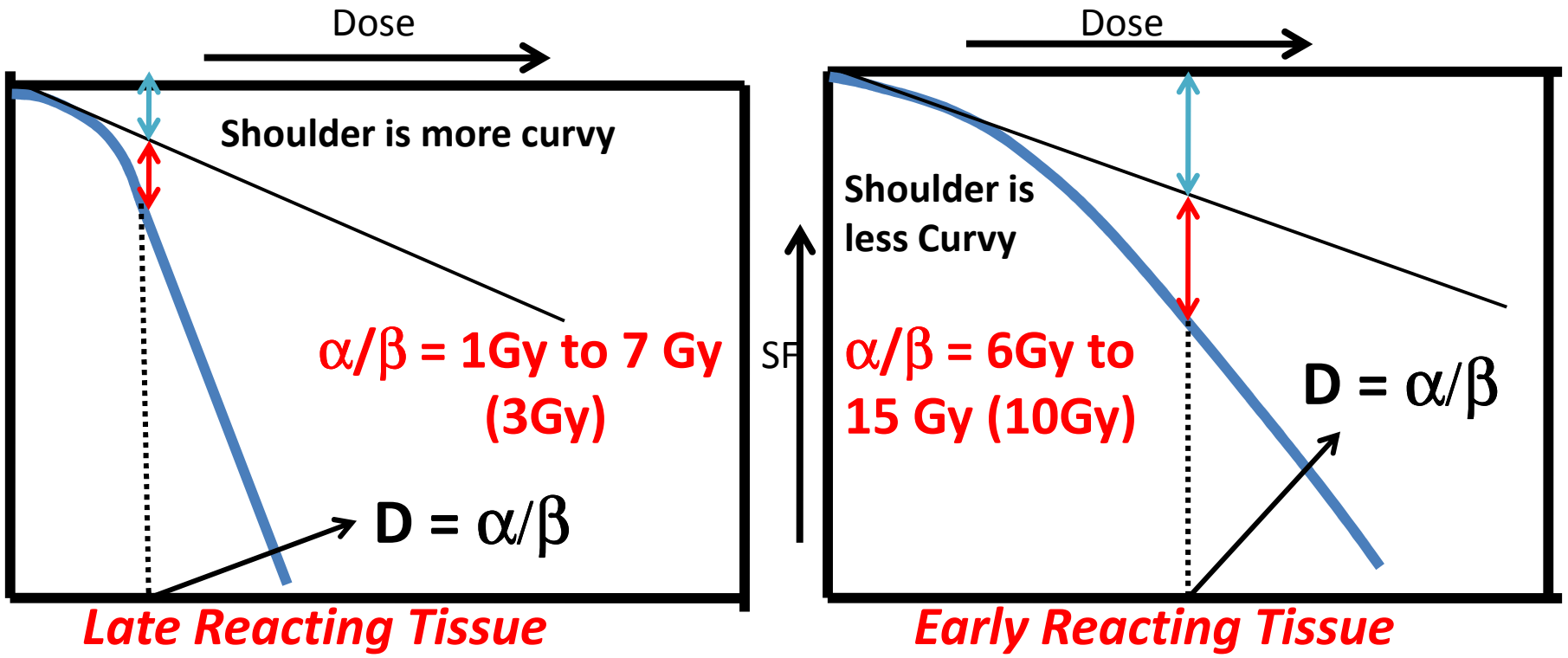
Linear Quadratic model (LQ Model)



➢ So α/β can be defined as the dose at which contribution by single hit (Linear) kill becomes equal to double hit (Quadratic) kill.

α/β Ratio defines "curviness" of survival curve

Based on α/β ratio, the body tissues have been divided into two category.



Calculated α/β ratios for some tissues

TABLE 22.1. *Ratio of Linear to Quadratic Terms From Multifraction Experiments*

Reactions	α/β, Gy
Early	
Skin	9–12
Jejunum	6–10
Colon	10–11
Testis	12–13
Callus	9–10
Late	
Spinal cord	1.7–4.9
Kidney	1.0–2.4
Lung	2.0–6.3
Bladder	3.1–7

Average 10

Average 3

Calculated α/β ratios for some tumors

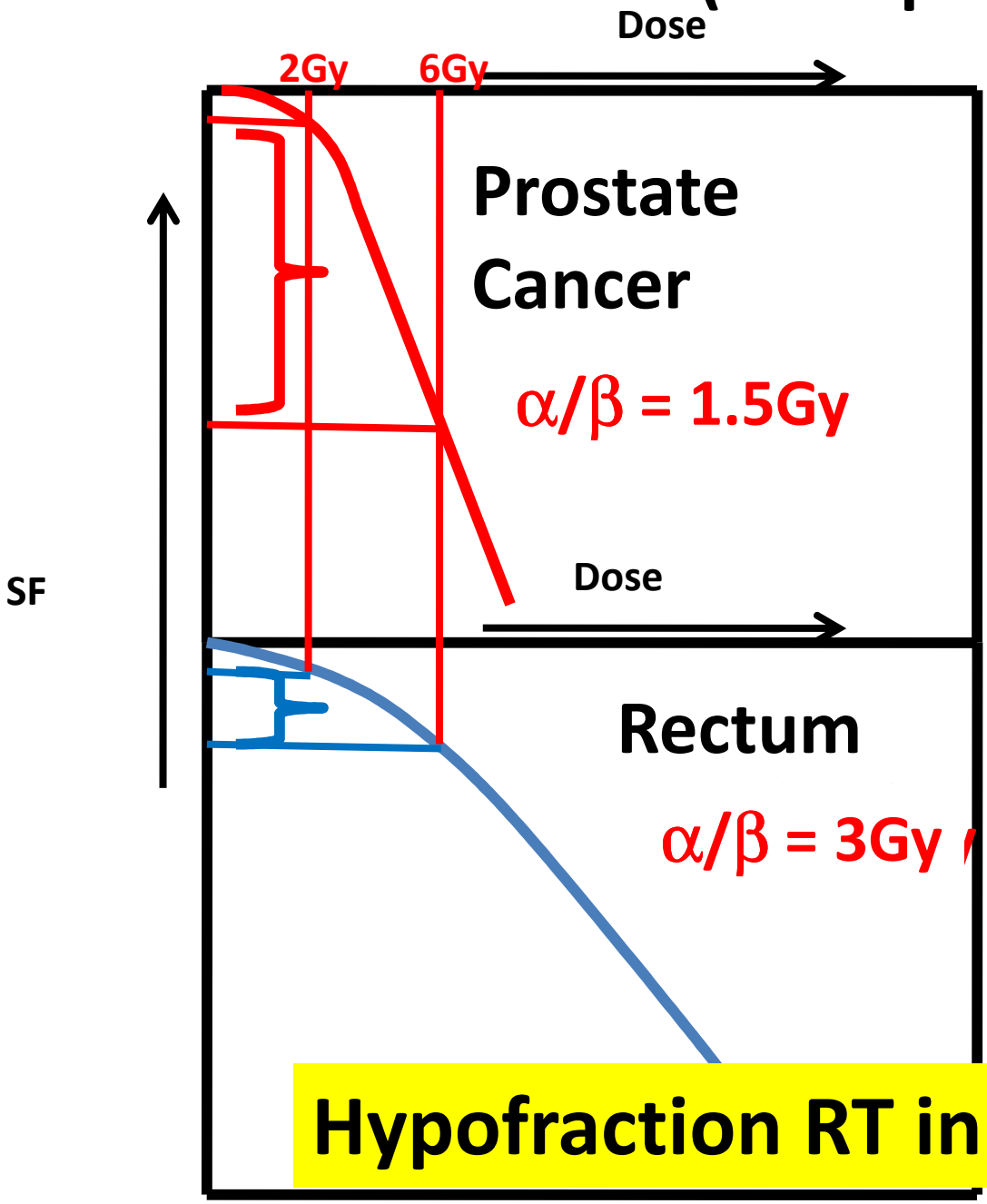
Tumors	
Head and neck: nasopharynx	16 (–11; 43) Gy
Vocal cord	~13 Gy
Buccal mucosa	~6.6 (2.9; ∞) Gy
Tonsil	7.2 (3.6; ∞) Gy
Larynx	14.5 (4.9; 24) Gy
Lung: squamous cell carcinoma	~50-90 Gy
Cervix: squamous cell carcinoma	>13.9 Gy
Skin	
Squamous cell carcinoma	8.5 (4.5; 11.3) Gy
Melanoma	0.6 (–1.1; 2.5) Gy
Esophagus	4.9 (1.5; 17) Gy
Liposarcoma	0.4 (–1.4; 5.4) Gy

Average 10

.ondon, 2009, Hodder Arnold.

Prostate **1.5**

Fraction size (Dose per fraction)



- Increase in dose per fraction damages the tissue with low α/β ratio more than Tissue with high α/β ratio.

- *We usually do not go more than 2 Gy per fraction*

Hypofraction RT in Prostate ca

Radiobiology of Prostate Cancer

	a/b Ratio	95% CI
Low dose rate brachytherapy	1.5 Gy	0.8-2.2
	1.49 Gy	1.25-1.76
EBRT + HD Brachytherapy	1.2 Gy	0.03-4.1

Brenner IJROBP 1999 43 1095 / 2002 52 6 : Fowler IJROBP 2001 50 1024

Phase III Trial of Conventional or Hypofractionated High Dose Intensity Modulated Radiotherapy in Prostate Cancer (CHHIP)

- Hypothesis: alpha/beta ratio in ca prostate may be low (1.5)

NAD
3m

Conventional	74Gy	37F	7.4w
Hypofractionated	60Gy	20F	4w
Hypofractionated	57Gy	19F	3.8w

Conventional versus hypofractionated high-dose intensity-modulated radiotherapy for prostate cancer: 5-year outcomes of the randomised, non-inferiority, phase 3 CHHiP trial

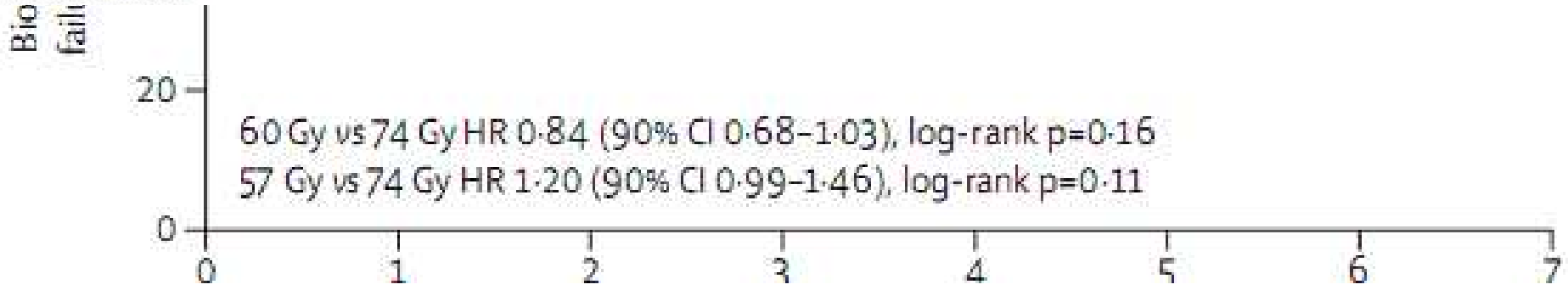
Lancet Oncol 2016; 17: 1047–60

60 Gy in 20F *BED = 180*

74 Gy in 37F *BED = 173*

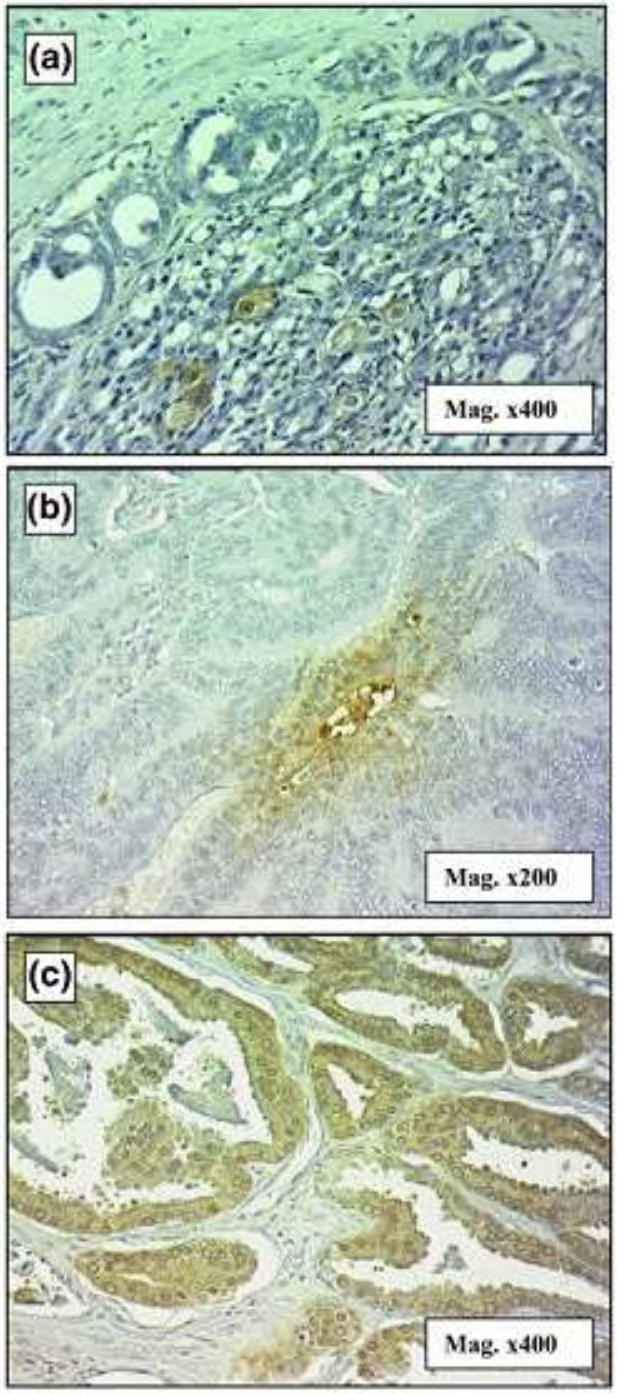
57 Gy in 19F *BED = 171*

Interpretation Hypofractionated radiotherapy using 60 Gy in 20 fractions is non-inferior to conventional fractionation using 74 Gy in 37 fractions and is recommended as a new standard of care for external-beam radiotherapy of localised prostate cancer.



Lancet Oncol 2016; 17: 1047–60

Hypoxia



Hypoxia assessment using Pimonidazole immunostaining in prostate carcinoma.

Carnell IJROBP 2006 65 91

(a) Pimonidazole uptake is seen within isolated malignant cells (<5%) : score 1+.

(b) Pimonidazole uptake scored 2+ is seen within 5%–15% of malignant cells surrounding a small area of necrosis.

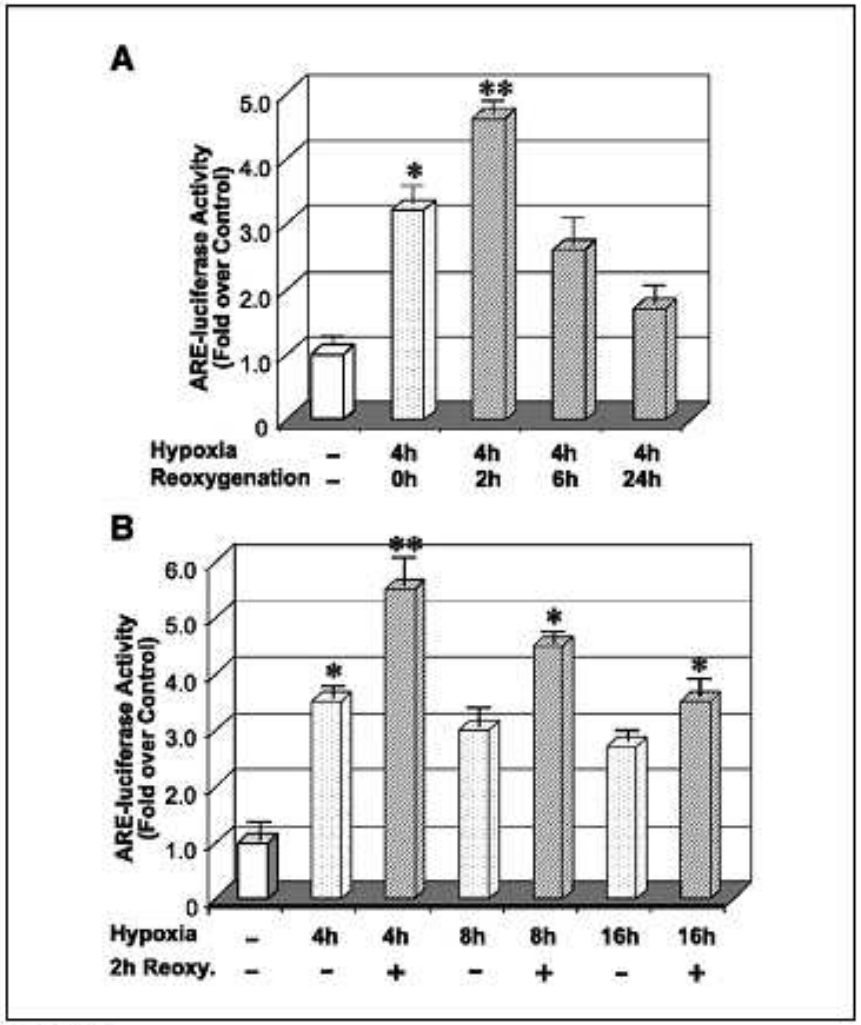
(c) 4+ pimonidazole uptake within both the nuclear and cytoplasmic compartments

Pimonidazole binding present in 92%(32/37) Ca

Correlation of 3+ staining with high Gleason score (p=0.04)

Hypoxia increases androgen receptor activity in prostate cancer cells.

Park, S.-Y. et al. Cancer Res 2006;66:5121-5129



Cancer Research

Gleason 7 -10

↓

Hypoxia

↓

Higher Androgen Activity

Patients with higher Gleason Score Treated with HT and RT will have better outcome

Conformal Radiotherapy with or without 3-6 months androgen suppression

1) Laverdiere JUROL 171 1137 2004, 2) D'Amico JAMA 292 821 2004 3) Pilepich IJROBP 2001 (50) 1243, 4)Denham Lancet Oncol 2005 6 841

	RT	RT +LHRHa	
7y PSA failure free survival	42%	66%	p≤0.01
5y PSA failure free survival	38%	52/56%	p≤0.002
5y survival free of salvage	57%	82%	p=0.002
5y survival free of salvage	63%	68/78%	p<0.03
8y Cause Sp survival	69%	77%	p=0.05

Thanks

Greetings From Shimla