

Bladder Cancer Basics and Treatment Decision Making



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Theme and Goals

- **Provide a practical guide for patients and families**
- **Inform and Empower**

FIGURE 1 Ten Leading Cancer Types for the Estimated New Cancer Cases and Deaths, by Sex, United States, 2008

Estimated New Cases*



51,230

		Males		Females			
Prostate	186,320	25%			Breast	182,460	26%
Lung & bronchus	114,690	15%			Lung & bronchus	100,330	14%
Colon & rectum	77,250	10%			Colon & rectum	71,560	10%
Urinary bladder	51,230	7%			Uterine corpus	40,100	6%
Non-Hodgkin lymphoma	35,450	5%			Non-Hodgkin lymphoma	30,670	4%
Melanoma of the skin	34,950	5%			Thyroid	28,410	4%
Kidney & renal pelvis	33,130	4%			Melanoma of the skin	27,530	4%
Oral cavity & pharynx	25,310	3%			Ovary	21,650	3%
Leukemia	25,180	3%			Kidney & renal pelvis	21,260	3%
Pancreas	18,770	3%			Leukemia	19,090	3%
All Sites	745,180	100%	All Sites	692,000	100%		

17,580

Estimated Deaths

9,500

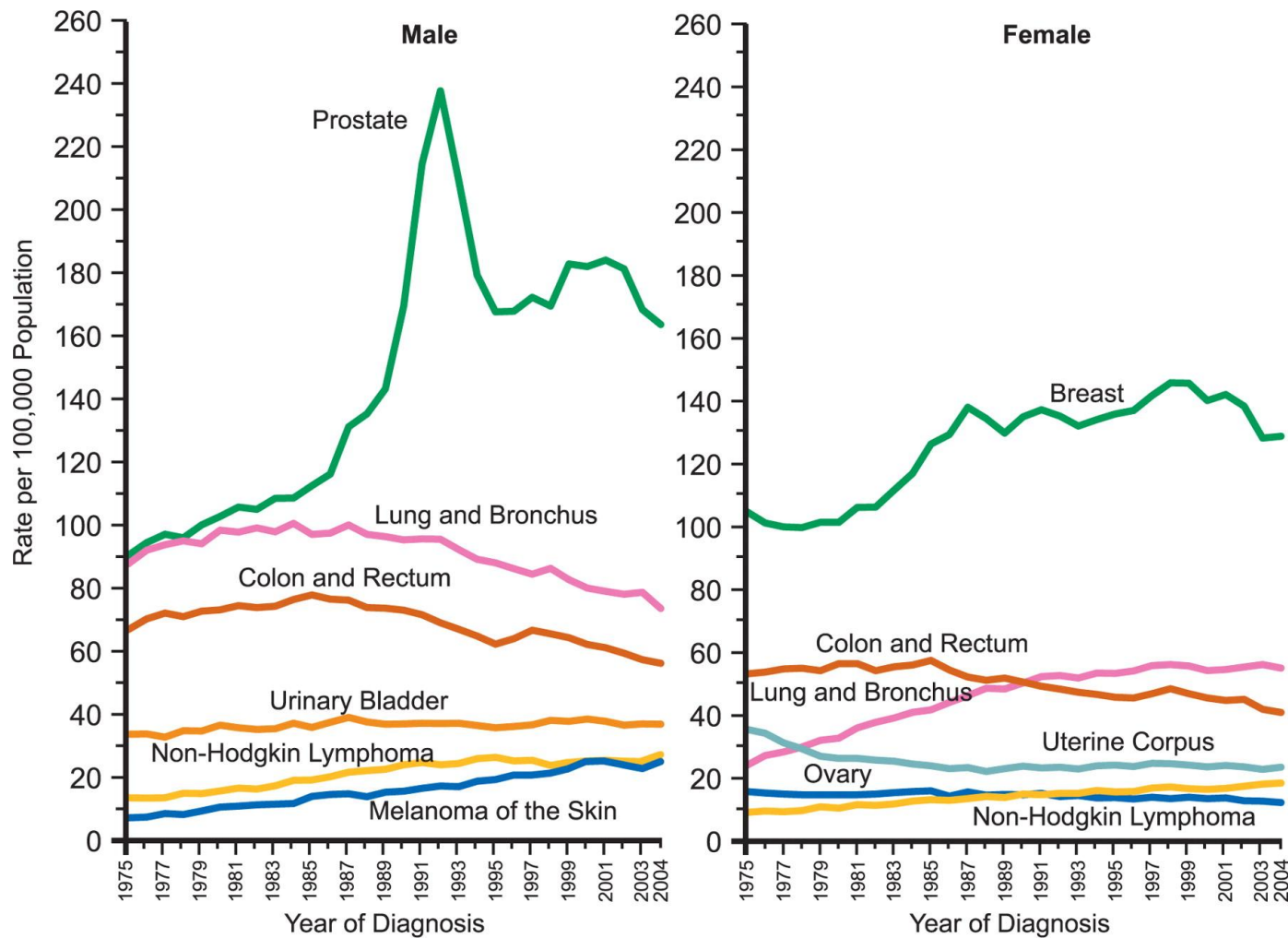
		Males		Females			
Lung & bronchus	90,810	31%			Lung & bronchus	71,030	26%
Prostate	28,660	10%			Breast	40,480	15%
Colon & rectum	24,260	8%			Colon & rectum	25,700	9%
Pancreas	17,500	6%			Pancreas	16,790	6%
Liver & intrahepatic bile duct	12,570	4%			Ovary	15,520	6%
Leukemia	12,460	4%			Non-Hodgkin lymphoma	9,370	3%
Esophagus	11,250	4%			Leukemia	9,250	3%
Urinary bladder	9,950	3%			Uterine corpus	7,470	3%
Non-Hodgkin lymphoma	9,790	3%			Liver & intrahepatic bile duct	5,840	2%
Kidney & renal pelvis	8,100	3%			Brain & other nervous system	5,650	2%
All Sites	294,120	100%	All Sites	271,530	100%		

4,150

From Jemal, A. et al.
CA Cancer J Clin 2008;0:CA.2007.0010v1-20070010.

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FIGURE 3 Annual Age-adjusted Cancer Incidence Rates* for Selected Cancers by Sex, United States, 1975 to 2004



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TABLE 13 Probability of Developing Invasive Cancers Within Selected Age Intervals by Sex, United States*

		Birth to 39 (%)	40 to 59 (%)	60 to 69 (%)	70 and Older (%)	Birth to Death (%)
All sites†	Male	1.42 (1 in 70)	8.58 (1 in 12)	16.25 (1 in 6)	38.96 (1 in 3)	44.94 (1 in 2)
	Female	2.04 (1 in 49)	8.97 (1 in 11)	10.36 (1 in 10)	26.31 (1 in 4)	37.52 (1 in 3)
Urinary bladder‡	Male	0.02 (1 in 4,477)	0.41 (1 in 244)	0.96 (1 in 104)	3.50 (1 in 29)	3.70 (1 in 27)
	Female	0.01 (1 in 9,462)	0.13 (1 in 790)	0.26 (1 in 384)	0.99 (1 in 101)	1.17 (1 in 85)
Breast	Female	0.48 (1 in 210)	3.86 (1 in 26)	3.51 (1 in 28)	6.95 (1 in 15)	12.28 (1 in 8)
Colon & rectum	Male	0.08 (1 in 1,329)	0.92 (1 in 109)	1.60 (1 in 63)	4.78 (1 in 21)	5.65 (1 in 18)
	Female	0.07 (1 in 1,394)	0.72 (1 in 138)	1.12 (1 in 89)	4.30 (1 in 23)	5.23 (1 in 19)
Leukemia	Male	0.16 (1 in 624)	0.21 (1 in 468)	0.35 (1 in 288)	1.18 (1 in 85)	1.50 (1 in 67)
	Female	0.12 (1 in 837)	0.14 (1 in 705)	0.20 (1 in 496)	0.76 (1 in 131)	1.06 (1 in 95)
Lung & bronchus	Male	0.03 (1 in 3,357)	1.03 (1 in 97)	2.52 (1 in 40)	6.74 (1 in 15)	7.91 (1 in 13)
	Female	0.03 (1 in 2,964)	0.82 (1 in 121)	1.81 (1 in 55)	4.61 (1 in 22)	6.18 (1 in 16)
Melanoma of the skin	Male	0.15 (1 in 656)	0.61 (1 in 164)	0.66 (1 in 151)	1.56 (1 in 64)	2.42 (1 in 41)
	Female	0.26 (1 in 389)	0.50 (1 in 200)	0.34 (1 in 297)	0.71 (1 in 140)	1.63 (1 in 61)
Non-Hodgkin lymphoma	Male	0.13 (1 in 760)	0.45 (1 in 222)	0.57 (1 in 174)	1.61 (1 in 62)	2.19 (1 in 46)
	Female	0.08 (1 in 1,212)	0.32 (1 in 312)	0.45 (1 in 221)	1.33 (1 in 75)	1.87 (1 in 53)
Prostate	Male	0.01 (1 in 10,553)	2.54 (1 in 39)	6.83 (1 in 15)	13.36 (1 in 7)	16.72 (1 in 6)
Uterine cervix	Female	0.16 (1 in 638)	0.28 (1 in 359)	0.13 (1 in 750)	0.19 (1 in 523)	0.70 (1 in 142)
Uterine corpus	Female	0.06 (1 in 1,569)	0.71 (1 in 142)	0.79 (1 in 126)	1.23 (1 in 81)	2.45 (1 in 41)

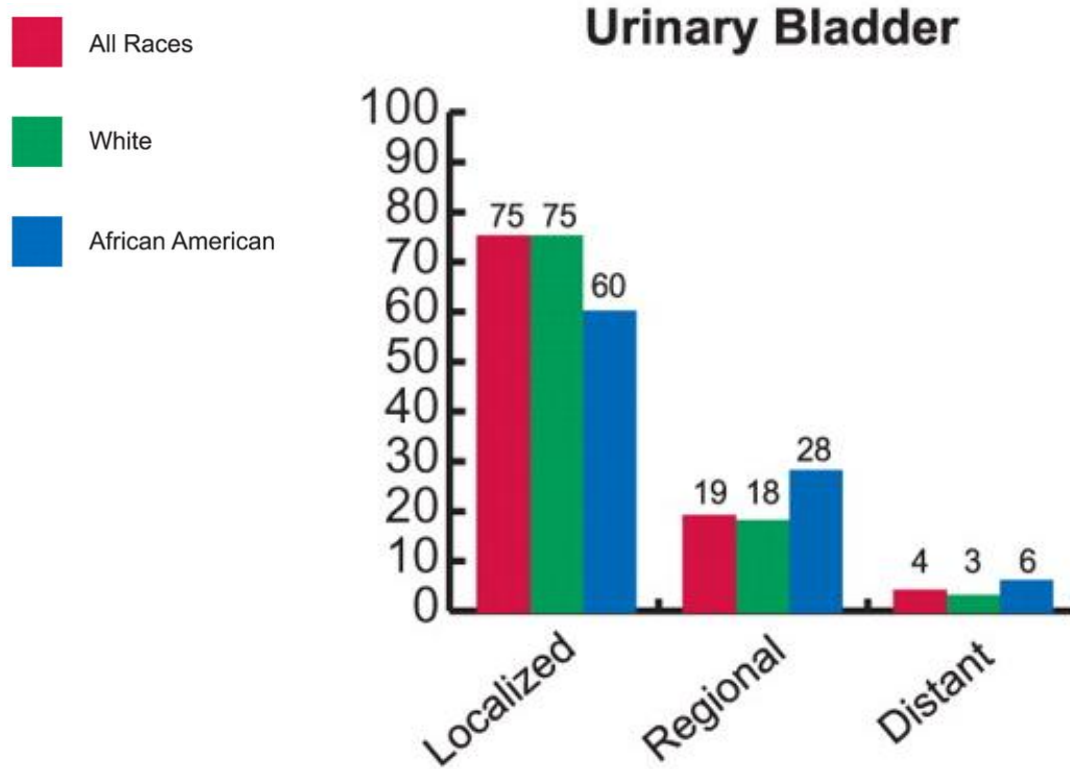
*For those individuals free of cancer at beginning of age interval.

†All sites excludes basal and squamous cell skin cancers and in situ cancers except urinary bladder.

‡Includes invasive and in situ cancer cases.

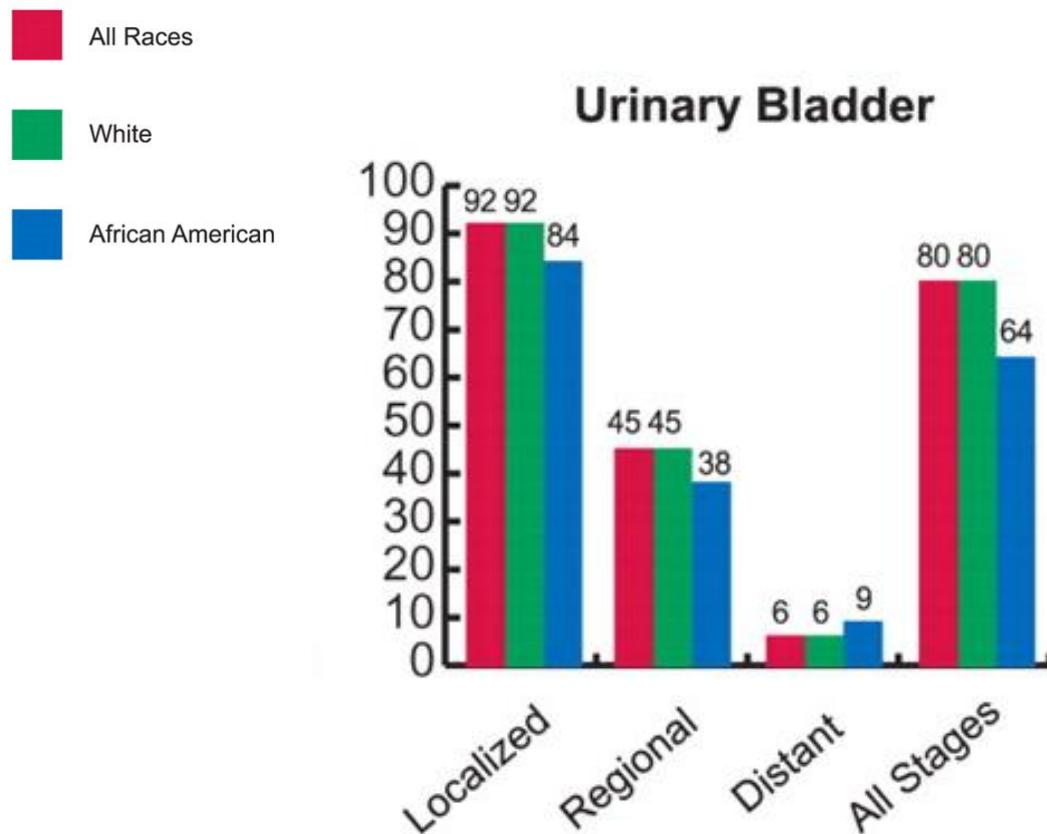
Source: DevCan: Probability of Developing or Dying of Cancer Software, Version 6.2.1. Statistical Research and Applications Branch, National Cancer Institute, 2007. www.srab.cancer.gov/devcan.

FIGURE 9 Distribution of Selected Cancers by Race and Stage at Diagnosis, United States, 1996 to 2003



From Jemal, A. et al.
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FIGURE 8 Five-year Relative Survival Rates Among Patients Diagnosed with Selected Cancers by Race and Stage at Diagnosis, United States, 1996 to 2003



From Jemal, A. et al.
CA Cancer J Clin 2008;0:CA.2007.0010v1-20070010.



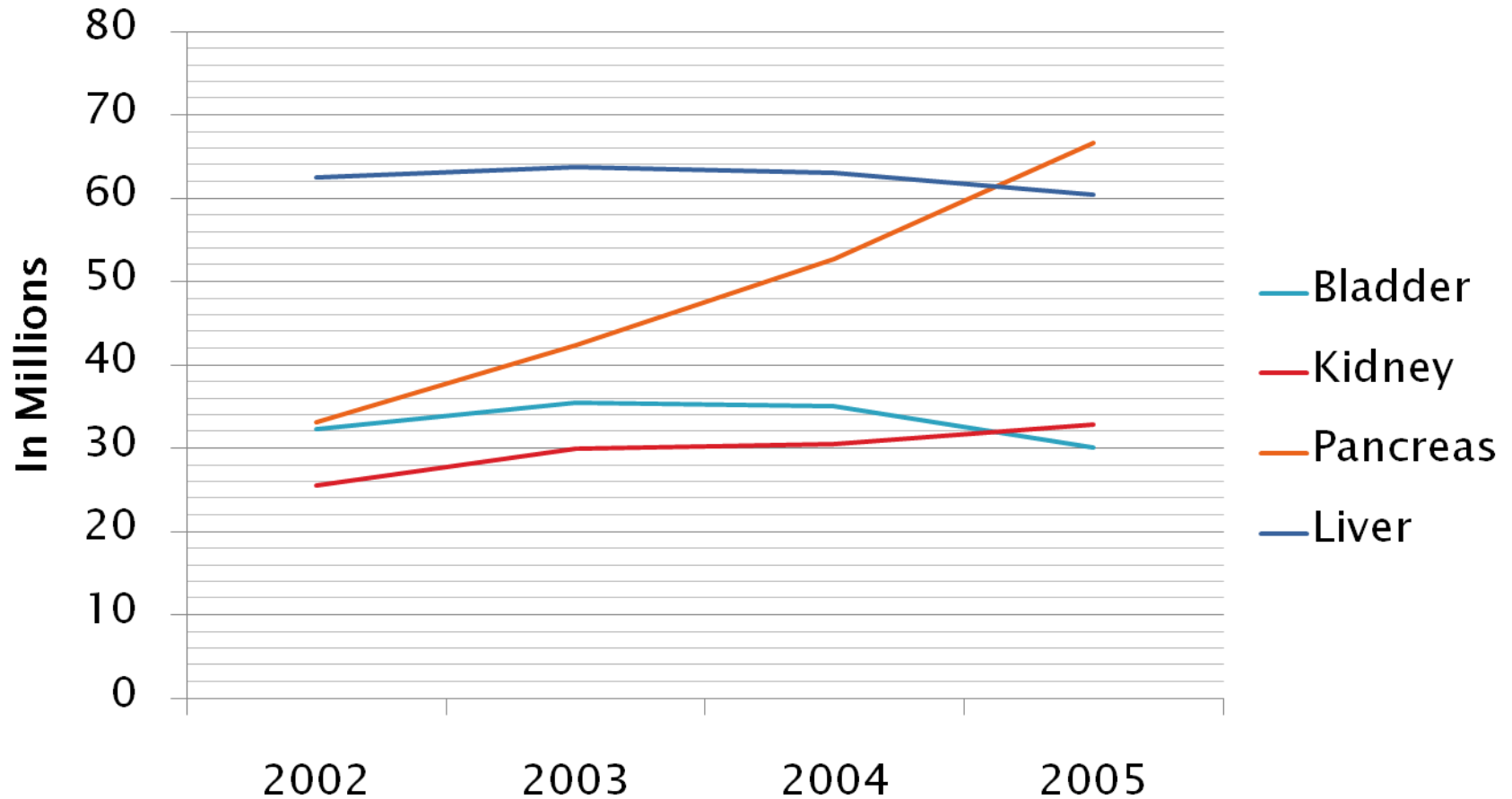
Prevalence And Importance

- 4th most common Ca in men
 - 11th most common Ca in women
 - 500,000 affected in US
 - The cost per pt from time of dx to death is the highest of any Ca in US
- Should be an important societal health policy issue

Funding of Research by Site

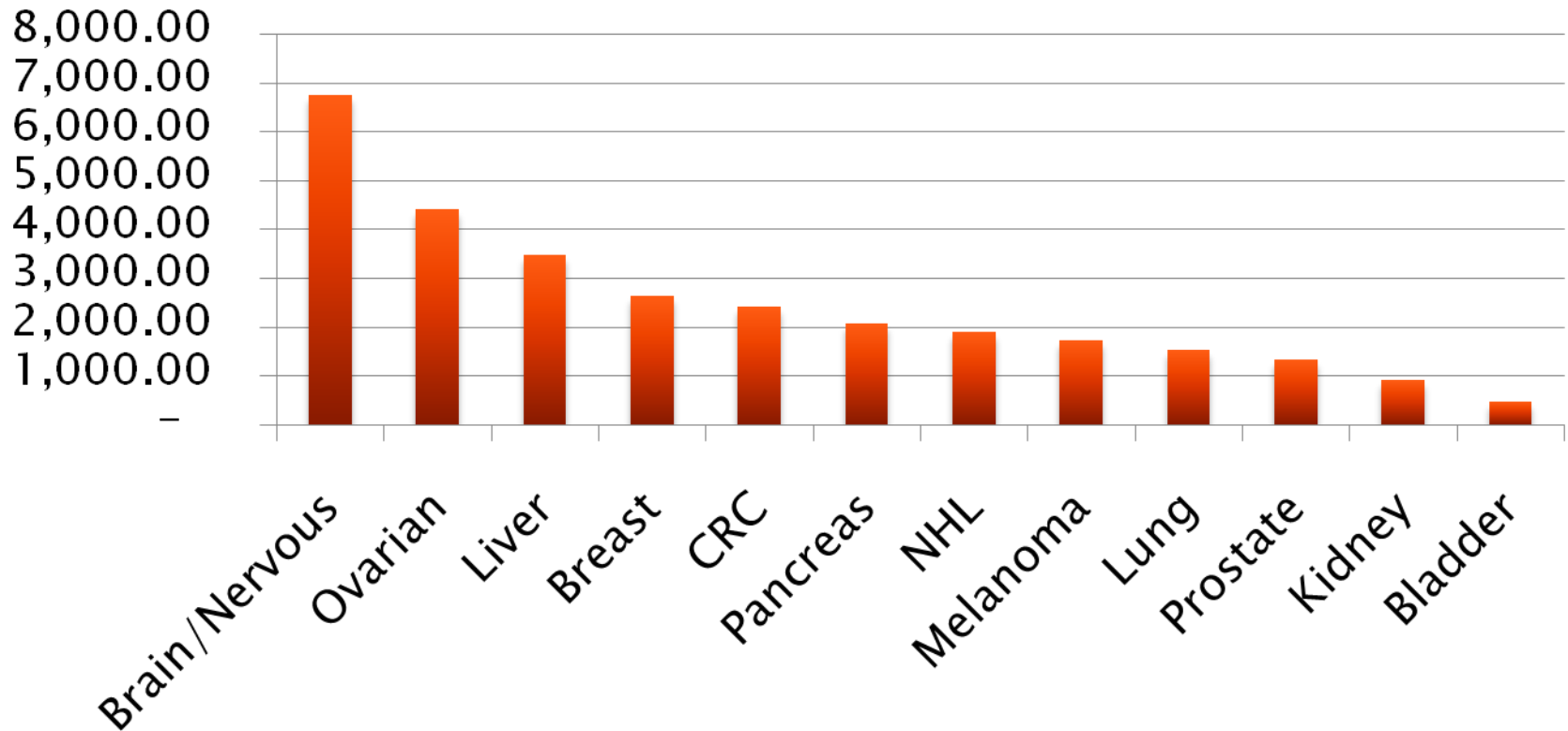
Primary Site	New (2007)	Deaths (2007)	Funding 2002	Funding 2003	Funding 2004	Funding 2005
Prostate	218,890	27,050	\$278.4	\$305.2	\$308.5	\$309.0
Lung	213,380	160,390	\$237.5	\$273.5	\$276.5	\$266.1
Breast	180,510	40,910	\$522.6	\$548.7	\$566.7	\$560.1
CRC	153,380	52,180	\$245.0	\$261.6	\$262.0	\$253.1
Bladder	67,160	13,750	\$32.3	\$35.5	\$35.1	\$30.1
NHL	63,190	18,660	\$85.6	\$95.2	\$99.6	\$107.0
Melanoma	59,940	8,110	\$82.3	\$90.7	\$94.9	\$102.9
Kidney	51,190	12,890	\$25.6	\$30.0	\$30.5	\$32.9
Ovarian	22,430	15,280	\$93.5	\$99.4	\$99.5	\$97.7
Liver	19,160	16,780	\$62.5	\$63.7	\$63.0	\$60.5
Pancreas	37,170	33,370	\$33.1	\$42.3	\$52.7	\$66.7
Brain/Nervous	20,500	12,740	\$95.2	\$111.5	\$132.3	\$124.9

NCI Research Funding By Year



NCI Cancer Research Funding for FY 2005

Dollars Per New Case (in \$M)



Risk Factors For Bladder Ca

- **Cigarette Smoking**
- **Occupational Exposure To Benzene
Organic Compunds**
 - *Rubber* - *Petroleum* -*Dyes*
- **Chronic Infection, Chronic Catheter**
- **Schistosomiasis Infection (Middle East)**

Presenting Symptoms

- **Gross Painless Hematuria**

- *Bladder Ca Until Proven Otherwise*

OR

- **Irritative Symptoms w/o Other Cause**

- *Neg Culture*

- *Often Has Hematuria*

- *Consider Urine Marker Studies*

Evaluation of Hematuria

Nieder #1082

- Surveyed 270 primary care MDs eval of hematuria:

	<u>micro</u>	<u>gross</u>
• Imaging	25%	41%
• Urol referral	36%	77%

Increased awareness of the assoc of hematuria w bladder ca is still needed to avoid delay in Dx

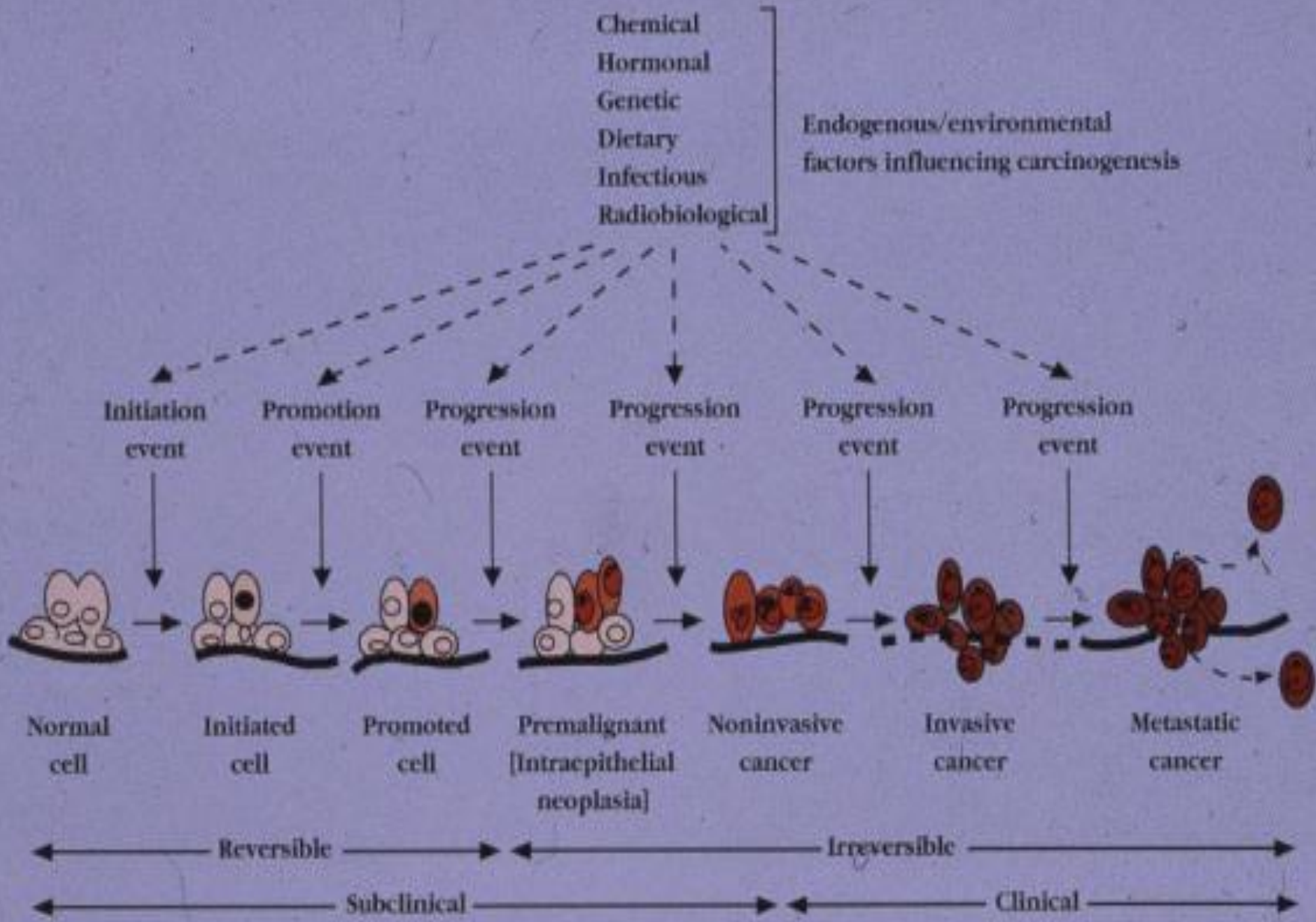


Figure 1. Multistep process of carcinogenesis

Bladder Ca: General Principles

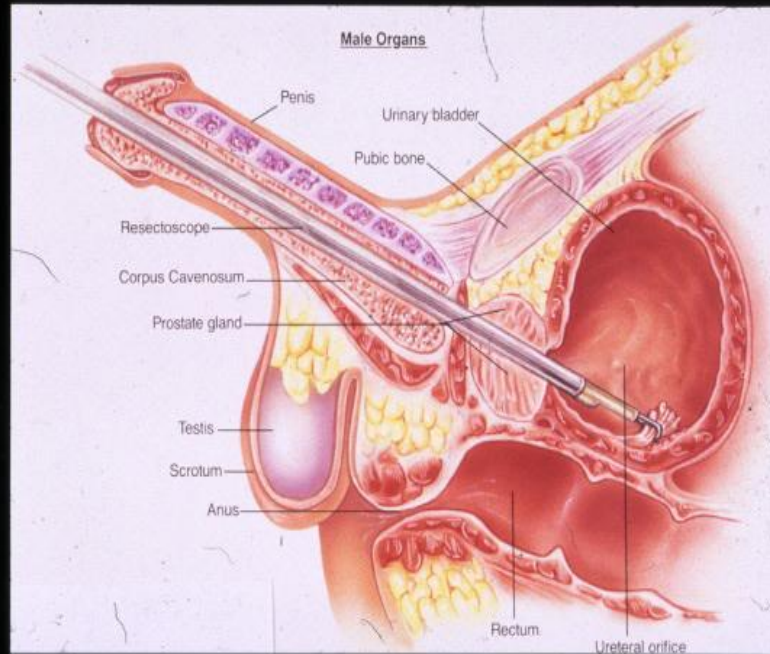
- **The Entire Urothelium Is Abnormal**
- **Multiple Recurrences Are Common**
(polychronotopism)
- **Serial F/U Important**
 - Urinalysis For Blood
 - Cystoscopy
 - Selective use of Urine Markers

Determinants Of Behavior

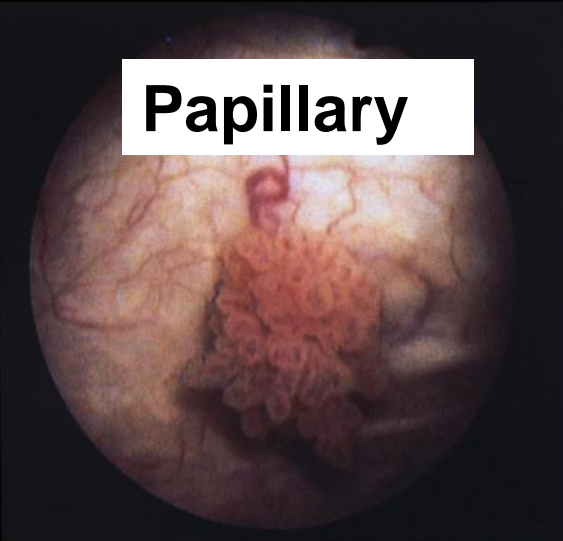
- **Grade:** low (1, 2*) vs high (2*, 3)
- **Stage:**
 - *Noninvasive: Ta, Tcis*
 - *Invasive: T1, T2, T3, T4*
- **Size**
- **Multifocality**
- **Variant Histology:**
 - Small Cell, Micropap, Squamous, Sarcoma*
- **Molecular:**
 - *Chromosomal* - *Genomic* - *Proteomic*

*Tumors Become Life-threatening When They Metastasize
(ie, invade lymphatics and veins)
T1 Is The Beginning Of Invasive Behavior*

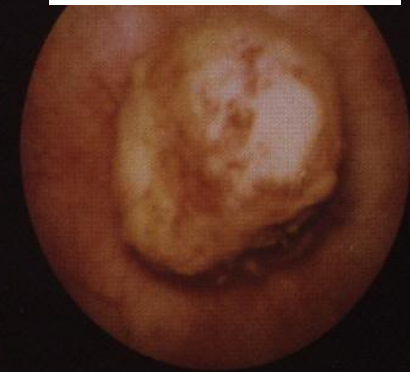
Cystoscopic Appearance



Papillary

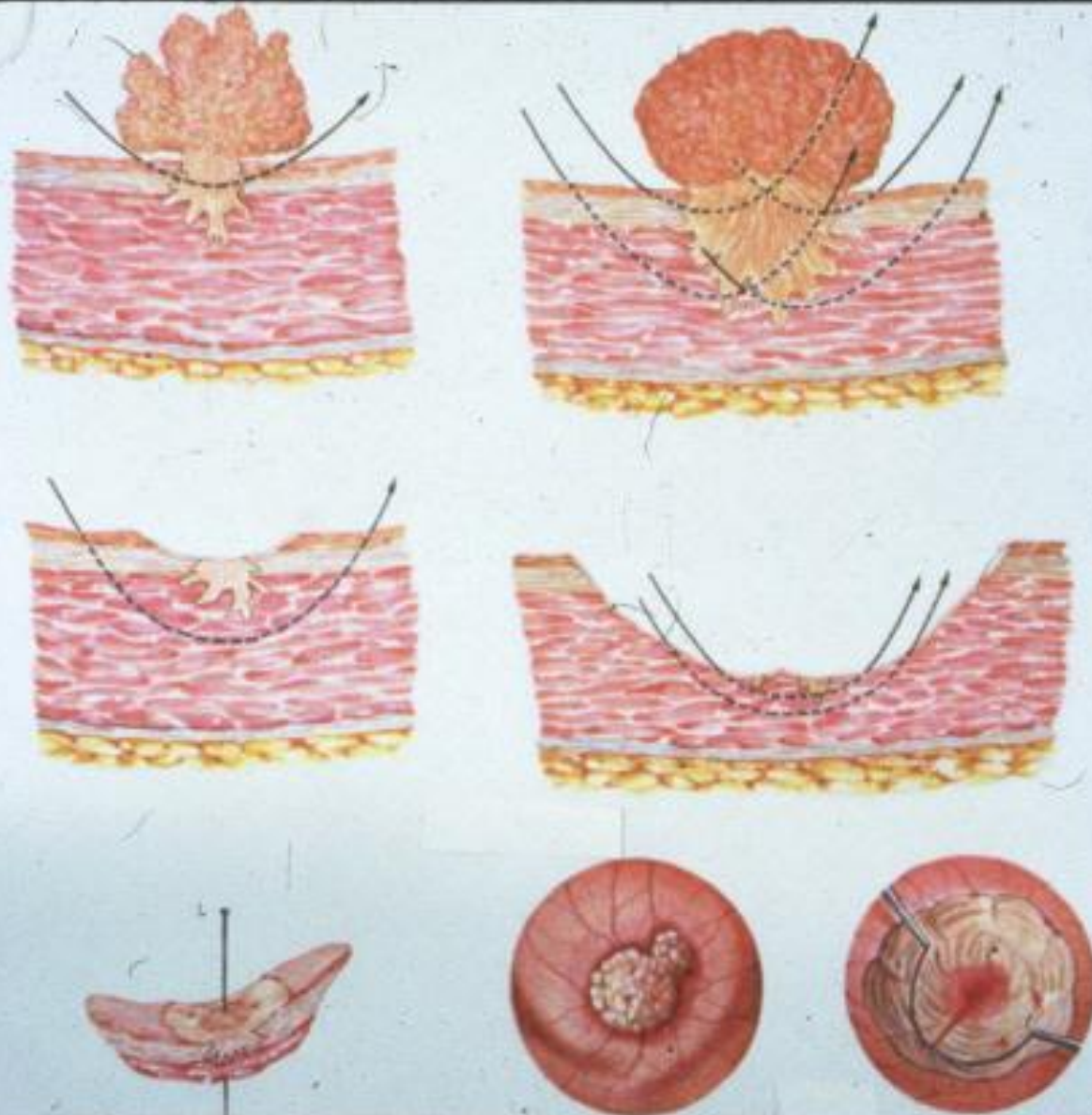


Nodular



Muscle-invasive tumour (cT2) on posterior bladder wall

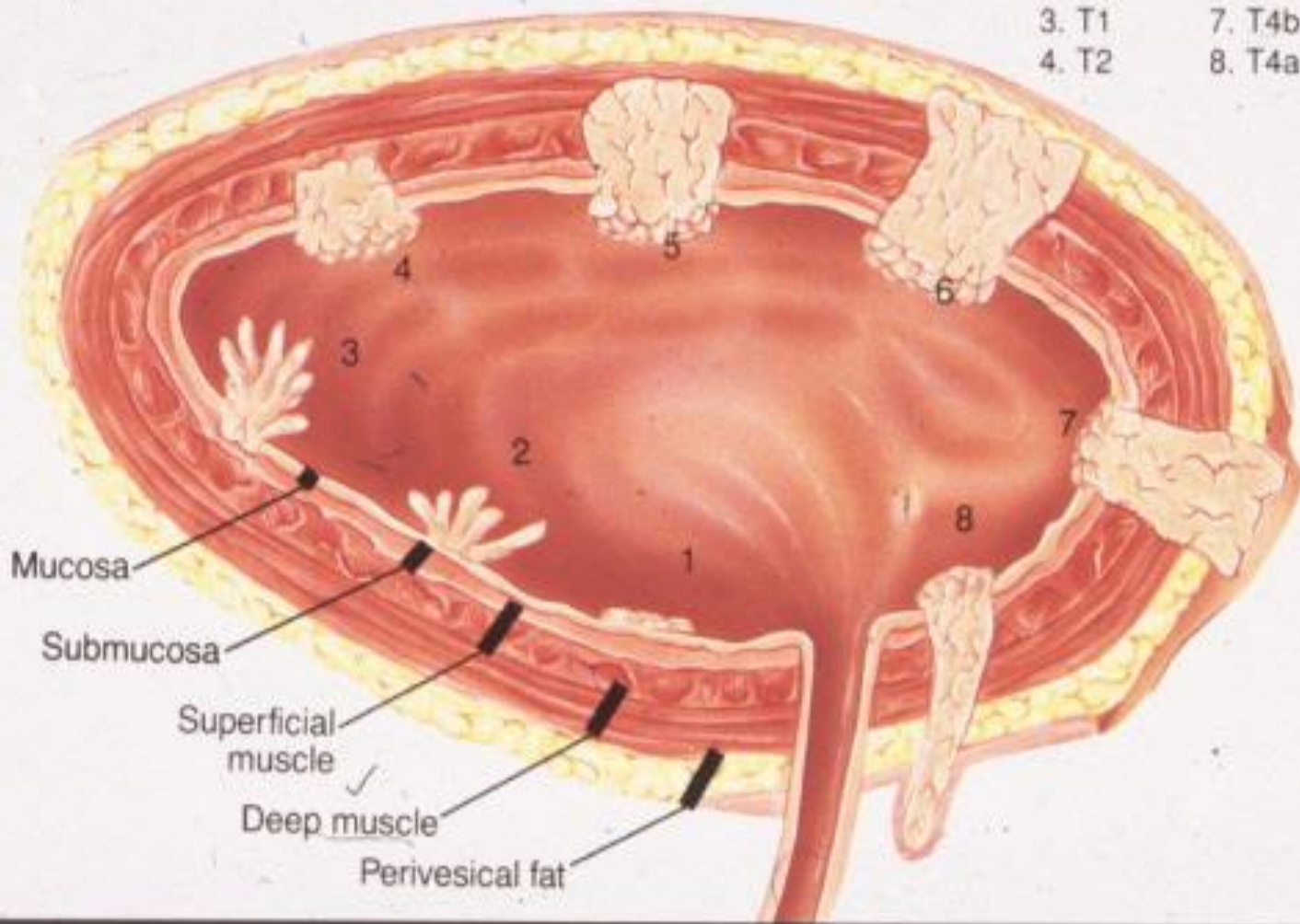
Importance of Depth of Biopsy / Resection



Bladder

TNM Classification

- | | |
|--------|--------|
| 1. Tis | 5. T3a |
| 2. Ta | 6. T3b |
| 3. T1 | 7. T4b |
| 4. T2 | 8. T4a |



Intravesical Therapy

- **Goals: prevent or delay recurrence and progression**
- **Who needs it?**
- **Induction Rx**
- **Maintenance Rx**
- **Importance of a perioperative dose of intravesical chemo (*never BCG*)**

Intravesical BCG Immunotherapy

- Consensus for:
 - 6 wk induction
 - host response begins after 3rd wk
 - maintenance Rx indicated
- However
- Optimal maintenance regimen is less clear

Restaging TURBT: Why ?

- Frequent incomplete removal of all tumor at initial TURBT may lead to ineffective intravesical Rx, higher tumor recurrence rate
- Frequent understaging may lead to inadequate initial Rx and increased risk of progression to invasion, systemic disease

Timing Of Cystectomy For G3T1

- Have we attempted intravesical Rx for too long ?
- When does risk/benefit ratio switch in favor of cystectomy ?
 - The pendulum is shifting to earlier cystectomy for a high proportion of G3T1

Restaging TURBT for G3,T1

- SUO panel
 - residual Tumor in > 50%
 - upstage to T2 in 20-30%

Restaging TURBT recommended for all G3,T1 unless features already indicate need for cystectomy

Invasive: G3,T1

Early cystectomy appears indicated in many pts w high grade, stage T1 disease:

- especially for T >3cm, multifocal, or w assoc CIS

Conclusions on Repeat TURBT & G3,T1

- For G3T1 the question we should be asking is not:
 - “ Is cystectomy necessary yet?”
- But rather:
 - “ **When is less than cystectomy adequate?**”

Invasive Disease

- **The ability to metastasize** (ie, LVI spread) **is what makes invasive disease life-threatening**
- **Lamina propria invasion (T1) is the beginning of invasive behavior; occasional LVI**
- **Muscularis propria invasion (T2) has frequent, early LVI**

Cystectomy is indicated for T2 and some (most?) T1 disease

Lymphovascular Invasion

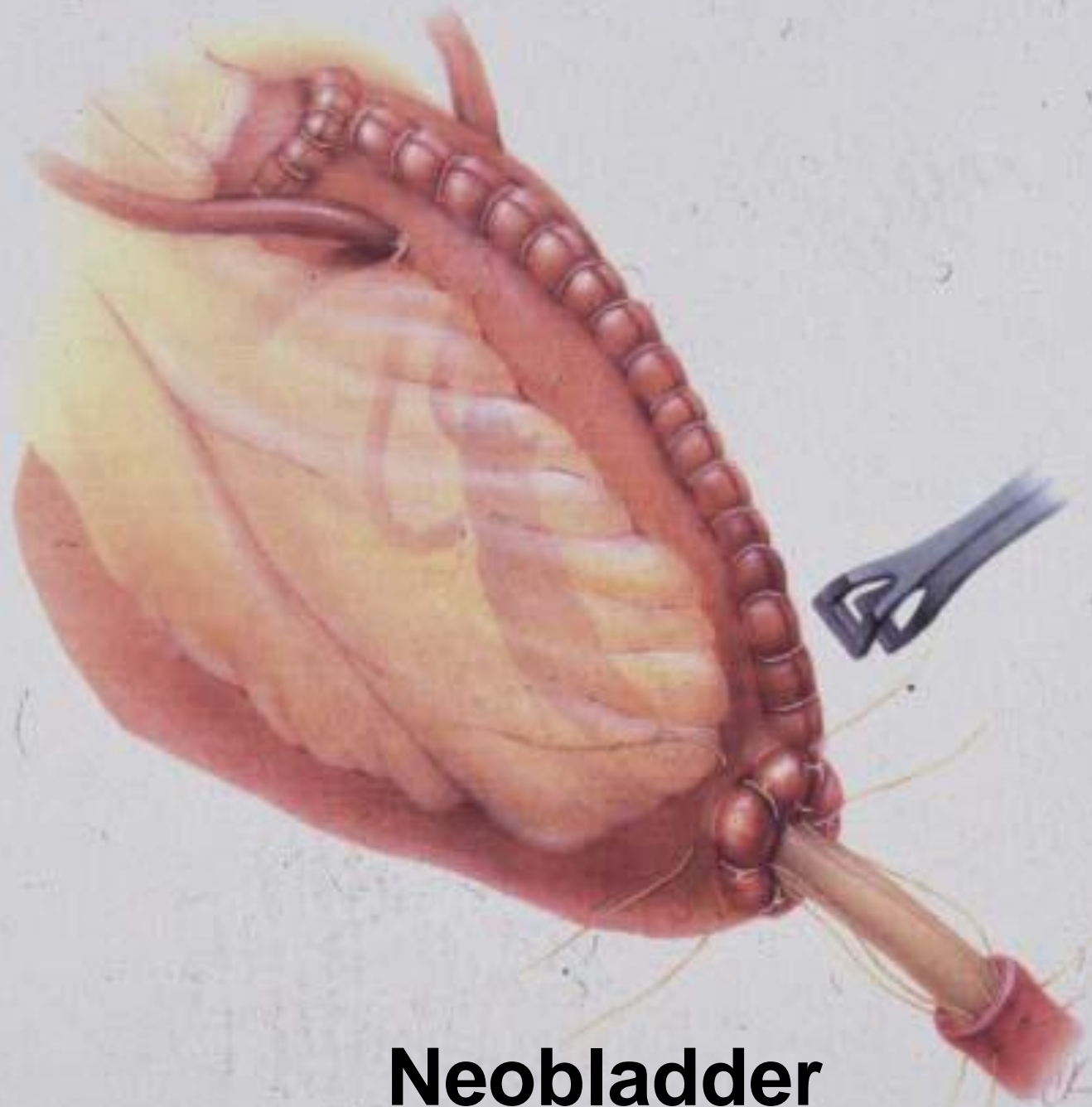
- **Kunju** Ab # 1520
 - Low concordance of LVI between TURBT & cystect; mainly due to underreporting on TURBT
 - LVI+ assoc w incr cystect pTstage
- **Palou** Ab # 1664
 - LVI+ was an independent predictor of DSS in 739 cystect, RR= 1.88, p=0.005
- **Luongo** Ab # 1665
 - LVI+ correl w decr overall & decr DSS in 431 cystect

LVI is a strong predictor of negative outcome

Quality of life cystectomy

Potency nerve sparing

An anatomical illustration of a cystectomy procedure. The bladder is shown in a reddish-pink color, surrounded by a network of blue and red blood vessels and yellowish nerves. A large, dark, fibrous structure, likely the prostate gland, is visible on the left side of the bladder. A surgical instrument, possibly a stapler or stapler, is shown in the upper left quadrant, positioned to resect the bladder. The surrounding tissue is depicted in various shades of brown and red, representing muscle and connective tissue. The overall scene is set against a dark, reddish-brown background.



Neobladder

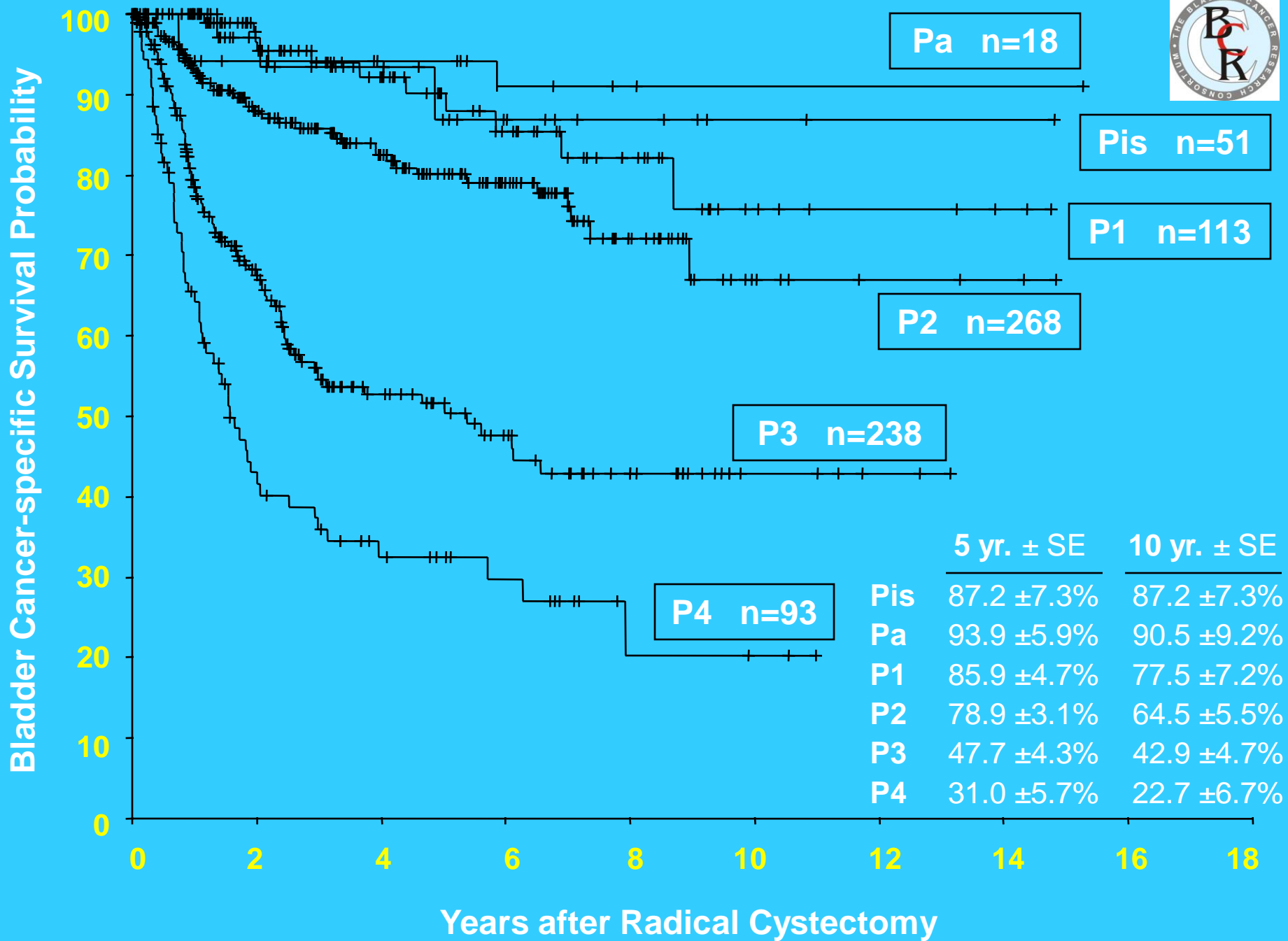
Voiding Cystourethrogram



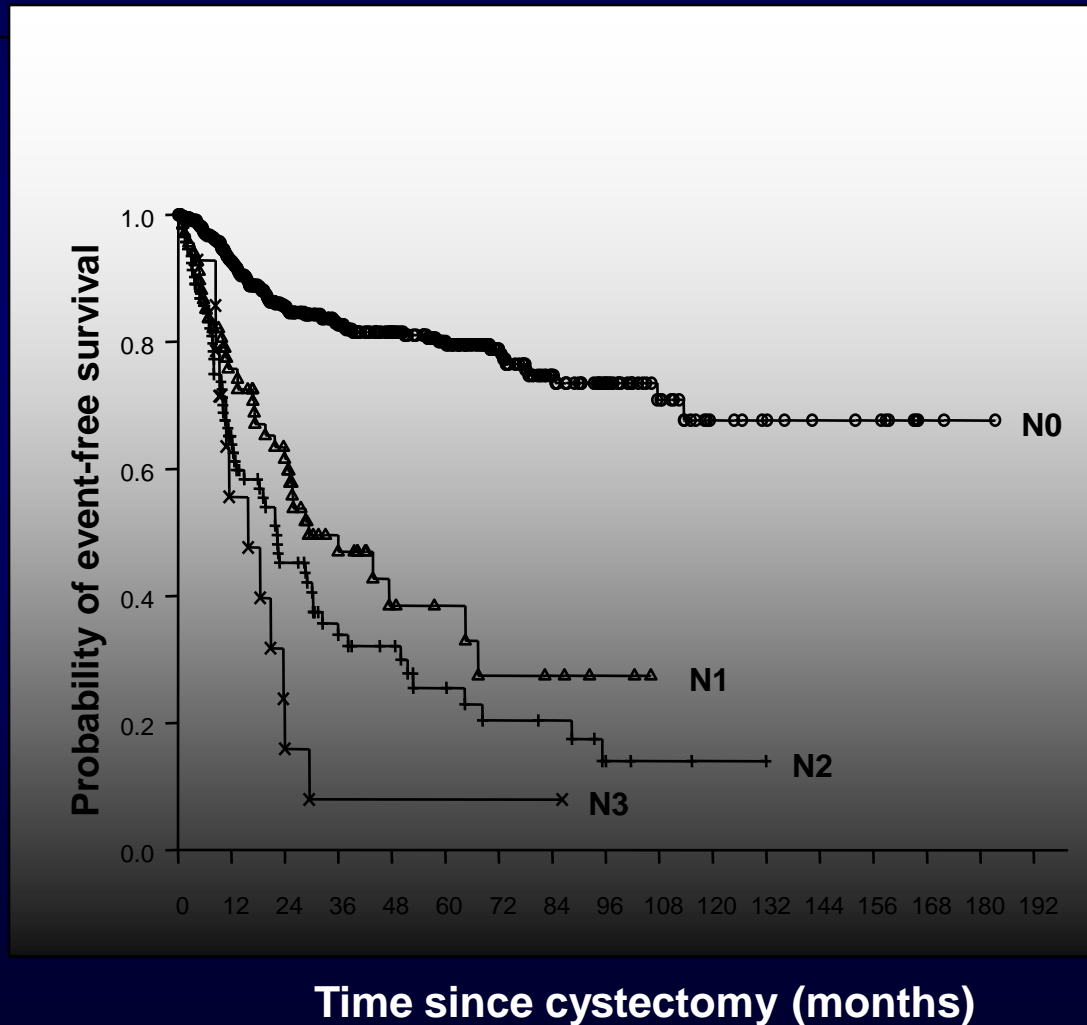
Can you tell it is a neobladder?

Cutaneous Reservoir





Disease-Specific Survival According to pN Stage at Cystectomy



Lymphadenectomy

- # 334 Ohar # 1650 Hollenbeck
- # 1653 Agarwal # 1667 Wright
- Extended lymphad assoc w:
 - incr LN+, & incr surv among LN+, & LN-
 - decr pos margins, decr recurrence
 - incr overall & disease specific survival
 - LND better predictor of outcome than
TNM staging

In Conclusion

- The extent and thoroughness of the pelvic lymphadenectomy for bladder cancer is an indirect surrogate for the quality of the surgery and its effectiveness, and **correlates with improved patient survival**

Treatment Options For Invasive Disease

- Radical cystectomy
- Partial cystectomy
- Turbt alone +/- intravesical therapy
- Turbt + Radiation
- “Trimodality” Therapy Blad Sparing
Turbt + Radiation + Chemotherapy

Conclusions On Bladder Sparing

- Blad sparing is a feasible alternative in a **select minority** of pts w invas blad ca:
 - Focal and completely resected
 - No hydronephrosis
- Satisfactory blad fx is retained in most pts
- @ 1/3 pts require subsequent cystect
- It is moderately effective for dis control (local and surv)
- Requires a committed multidisciplinary team approach
- Urologists should discuss it as a Rx option in appropriate pts

Conclusions on Bladder Sparing

- Bladder sparing results (local relapse, surv) **DO NOT** match those for contemporary radical cystectomy w extended lymphad at high volume centers of excellence for comparably matched groups of patients

Sagalowsky's Take-Home Messages On Current Treatment of Invasive Bladder Cancer

- With current limitations in Dx, staging, risk stratification, the major limitation to improving surv for pts w invas blad ca is that disease is all too frequently *systemic*
- *Earlier use* of systemic Rx is indicated

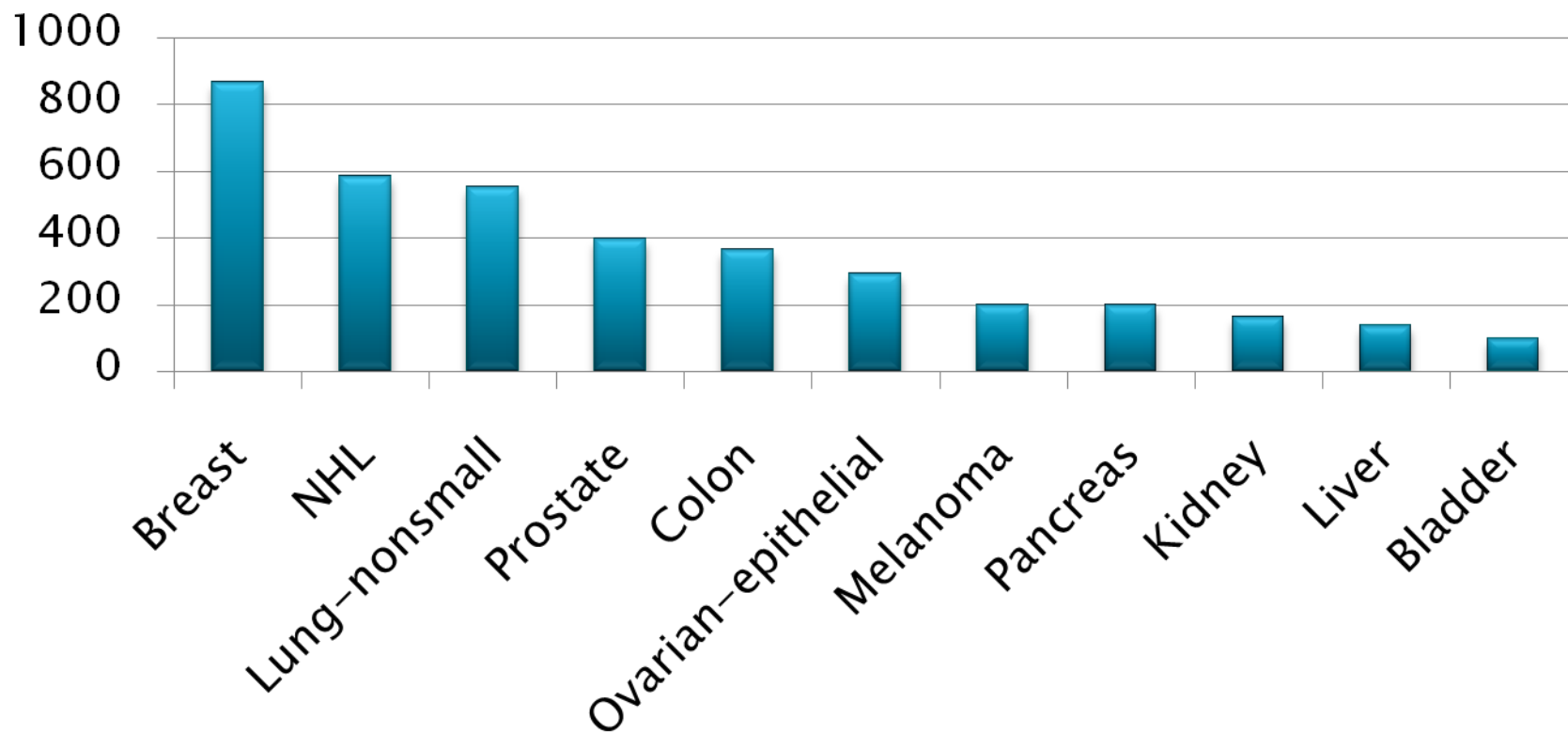
THANK YOU

Panel:
**New Directions For Improved
Treatment**

Number of Clinical Trials

As of July 30, 2007

By Site



Hypothesis

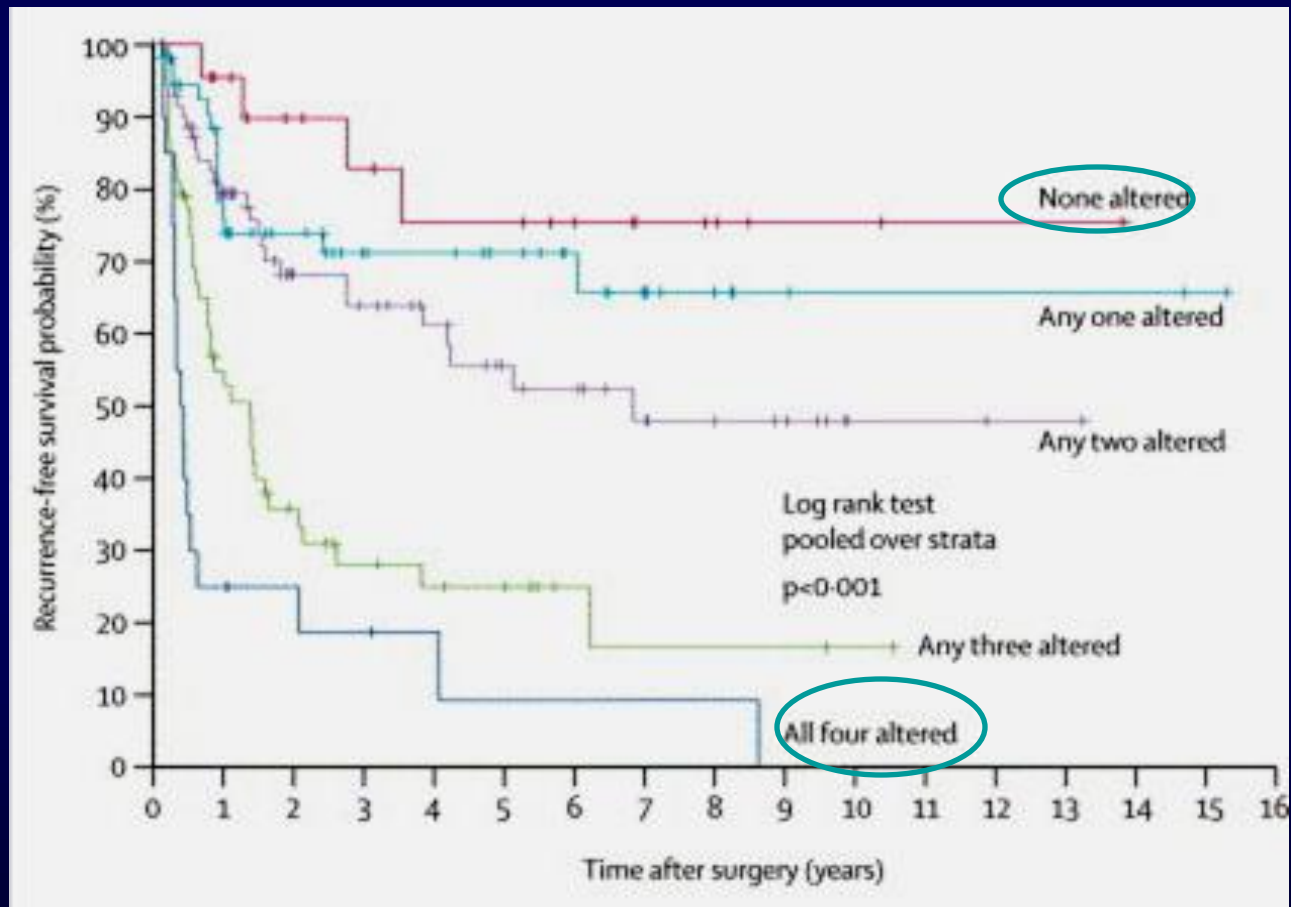
- To improve outcomes for pts w invas bladder ca we need:
 - Earlier dx while still organ confined, or
 - Better staging to identify nonorgan confined, or
 - More effective systemic Rx
- Another approach is to consider that the failure to show clear benefit of neoadj & adj chemoRx is due to failure to identify inherent tumor heterogeneity
 - ie, **Molecular “staging” of risk stratification**

Molecular Risk : Apoptotic Markers

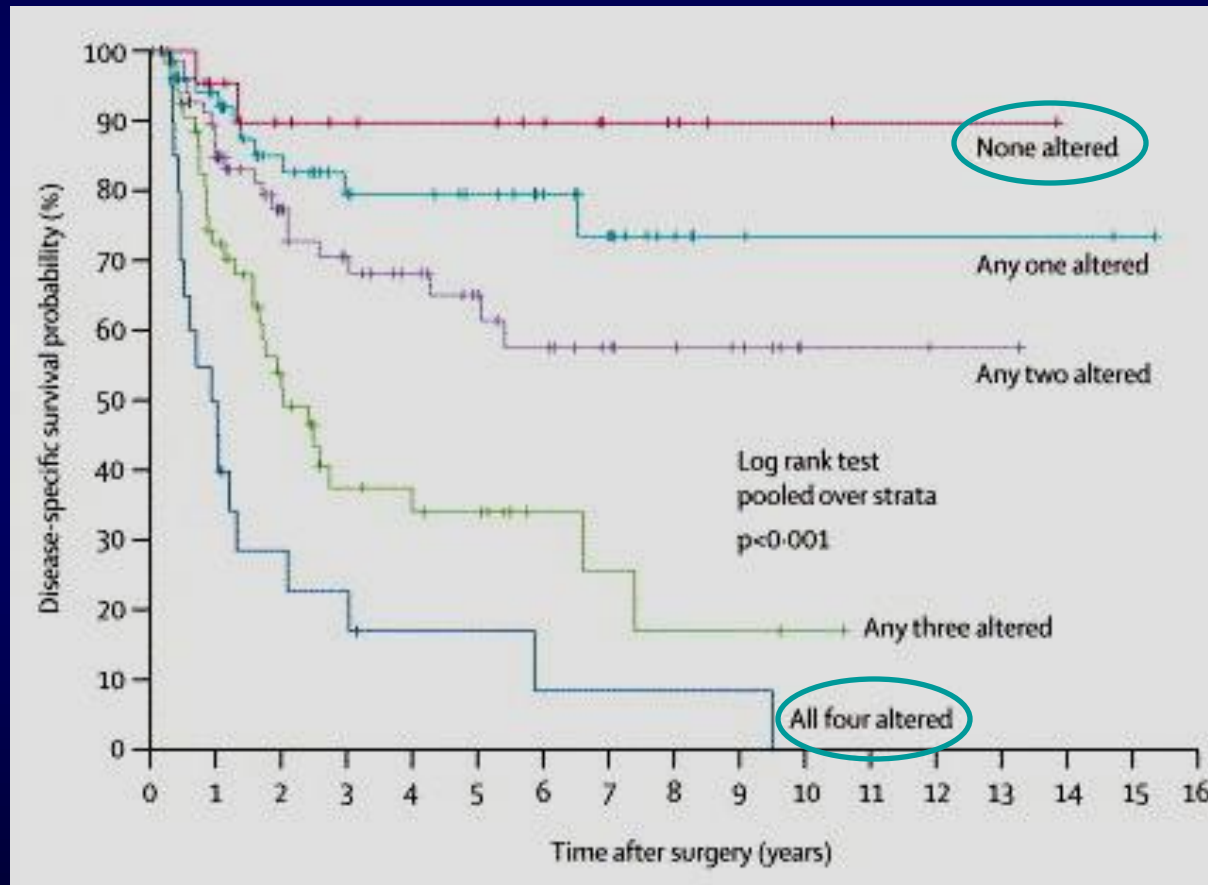
Karam # 238

- **226 cystect cases**
- **Studied a microarray panel of 4 apopt markers: Bcl-2, Caspace 3, p53, survivin**
- **Correlated marker abnormality w:**
 - **Recurrence free survival**
 - **Disease free survival**

Recurrence-Free Survival



Disease-Specific Survival



Molecular Risk Stratification

- **Extensive ongoing research on molecular predictors of cell cycle regulation:**

Apoptosis, Survivin, Methylation, TKIs, MMP, Cadherin, Angiogenic factors, Transcription regulators, Oncogenes, Suppressor genes

- **These will be the basis for targeted Rx**
- **However, application of these for pt care (intensity of f/u, and therapy) awaits prospective validation of correlations with disease outcome**