Bladder Cancer, 2006
Overview and Current Treatment

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Bladder Cancer Statistics, 2006

- New Cases: 61,460
  - 44,690 Men - 16,730 Women
- 3:1 Men to Women
  - 50% over age 73
- Estimated Deaths: 13,060
  - Men: 8,990 - Women: 4,070
- Incidence/Mortality: 20.8%
  - Men: 20% - Women: 24%
- Prevalence: More than 500,000 in US

Bladder Cancer Etiology

- Initial link - aniline dyes made in 1895
- Industrial exposure - rubber & textiles
- Aromatic amines - 30 x risk
- Tobacco - 3 x increased risk - 60% of cases
- Treatment Complication - 9 x risk with cyclophosphamide or ifosfamide - 4 x RT
- Schistosoma hematobium, infection, foreign body: squamous cell carcinoma

Diet and Bladder Cancer Risk: A Meta Analysis

- 40% increased risk for diets low in fruit: (HR 1.40, 95%: 1.08-1.83)
- 16% increased risk for diets low in vegetables: (HR 1.16, 95%: 1.01-1.34)
- 37% increased risk for diets high in fat (HR 1.37, 95%: 1.16-1.83)
- No increased risk for increased meat or reduced Vitamin A

Steinmaus CM:Am J Epidemiol. 2000 151:693-702.
Diet and bladder cancer: a meta-analysis of six dietary variables.

Bladder Cancer Pathology

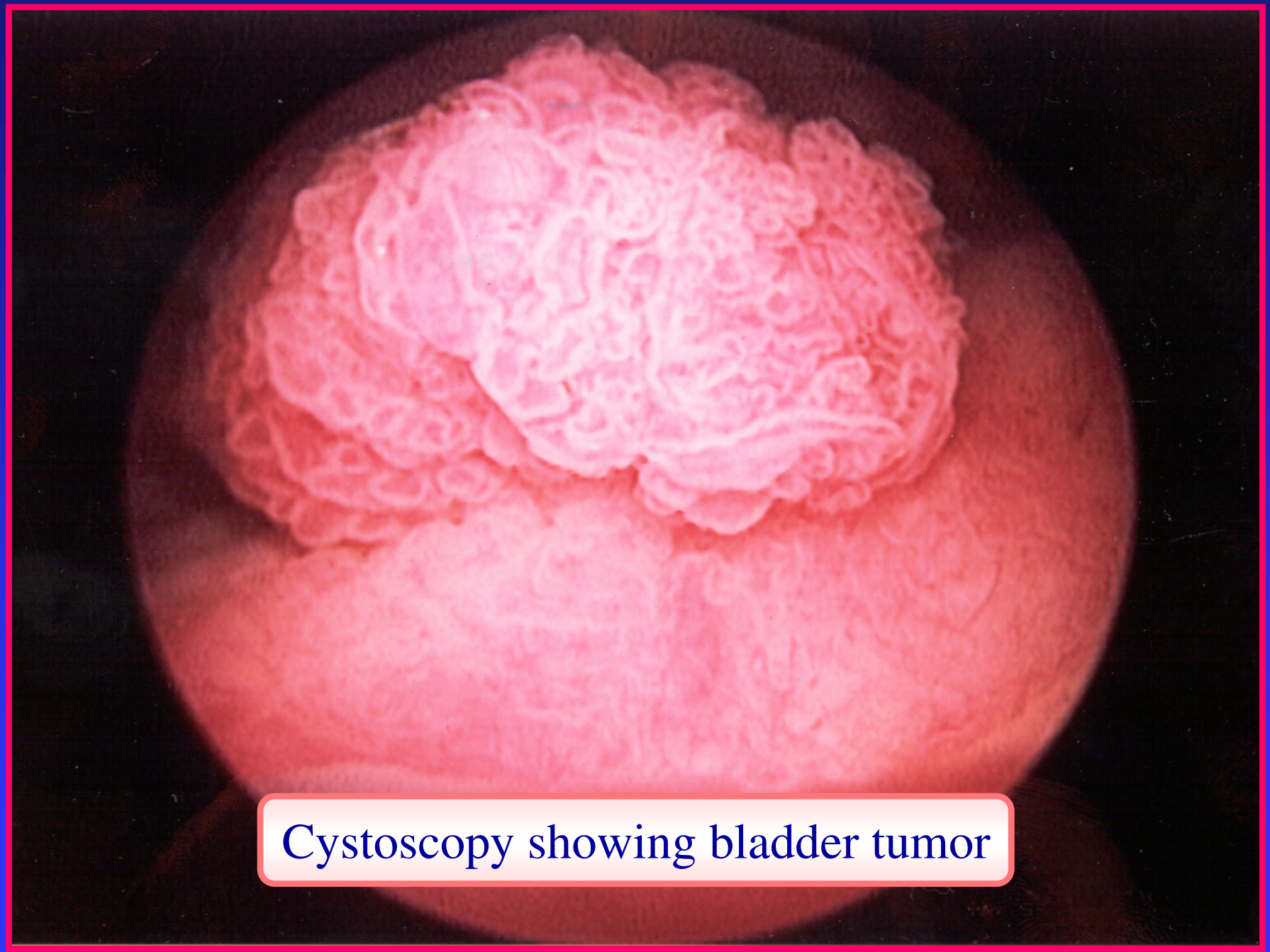
Transitional Cell 94%
Squamous Cell 5%
Adenocarcinoma <1%
Rhabdomyosarcoma <1%

Bladder Cancer
Signs and Symptoms

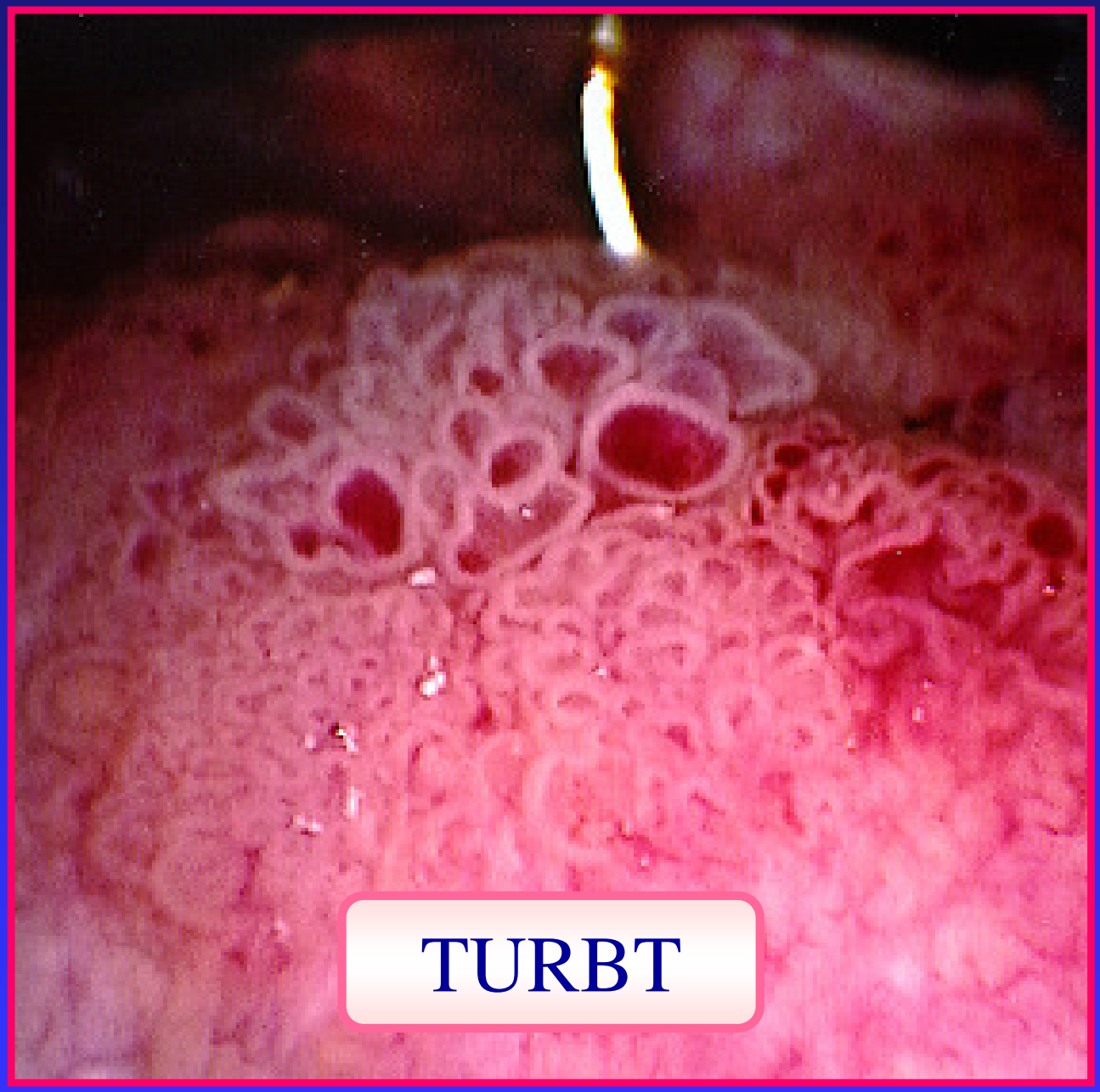
- 85% present with gross or microscopic hematuria
  - Bleeding is typically intermittent and not related to grade/stage
- 20% have irritative voiding symptoms burning, frequency
  - More commonly associated with CIS and high grade tumors

Diagnosis

- Cystoscopy is key
  - Papillary tumors are easily seen
  - High grade, solid, flat or in situ tumors may not be seen
- Urinary Cytology
  - 80% + sensitivity in high grade tumors with 95% specificity
  - Sensitivity improved with FISH
- IVP, CT scan for upper tract evaluation



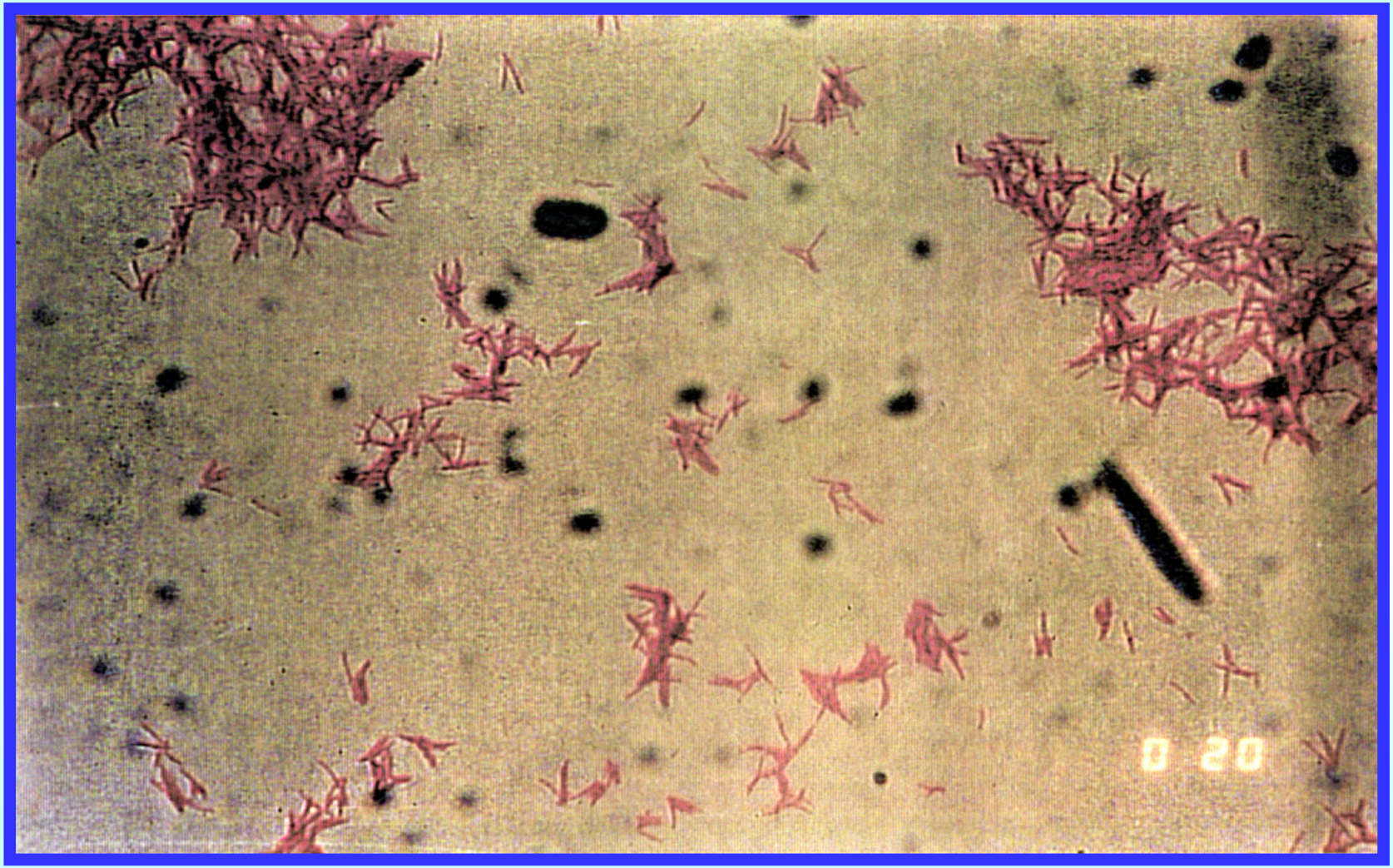
Cystoscopy showing bladder tumor


TURBT

Bladder Cancer: Natural History

- About 70% present with resectable, superficial tumors
  - but up to 88% recur within 15 years
- Patients can and should be monitored with cystoscopic examination at regular intervals to directly assess disease status
- Accessible for disease assessment
  - Topical and systemic treatment

BCG



Jean-Marie Camille Guérin (1872-1961)

BCG Past

Albert Calmette 1863-1933

1800-1900

- Majority of adults infected with tuberculosis - 25% mortality

1884

- Kock demonstrates M. tuberculosis causes TB

1894

- Calmette & Guerin begin race for vaccine in Lille, France at Institute Pasteur

1904

- Nocard isolates virulent bovine tuberculosis strain that is to become BCG

1921

- 13 years and 231 passages later- avirulence
- July given to newborn infant born to mother with active TB

BCG Past

1929

- Pearl in autopsy studies notes protective effect of TB against cancer

1935

- Holmgren in Sweden is first to treat cancer in humans with some success in 28 pts.

1936

- Rosenthal - BCG stimulates reticuloendothelial system

1959

- Old/Clarke (US) and Halpern (France) - BCG inhibits experimental tumors in animals

BCG Past
Lubeck, Germany BCG Tragedy

1930

- 70 infants died in Lubeck, Germany
- BCG implicated in deaths
- Doctors accused;

  later proven to be cross contamination with wild tuberculosis

BCG Past

1972

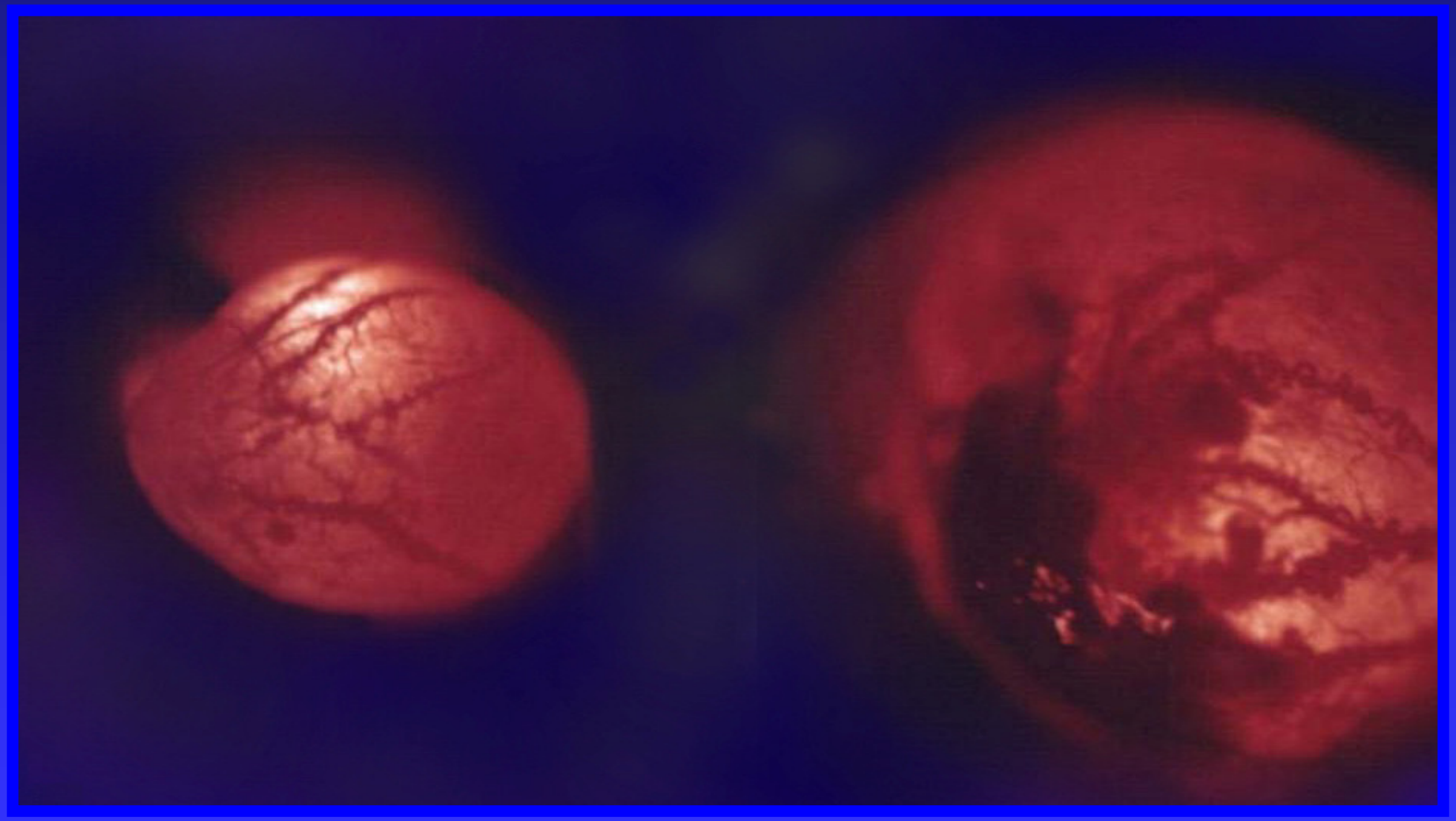
- Rosenthal - significant reduction in leukemia mortality in BCG vaccinated babies

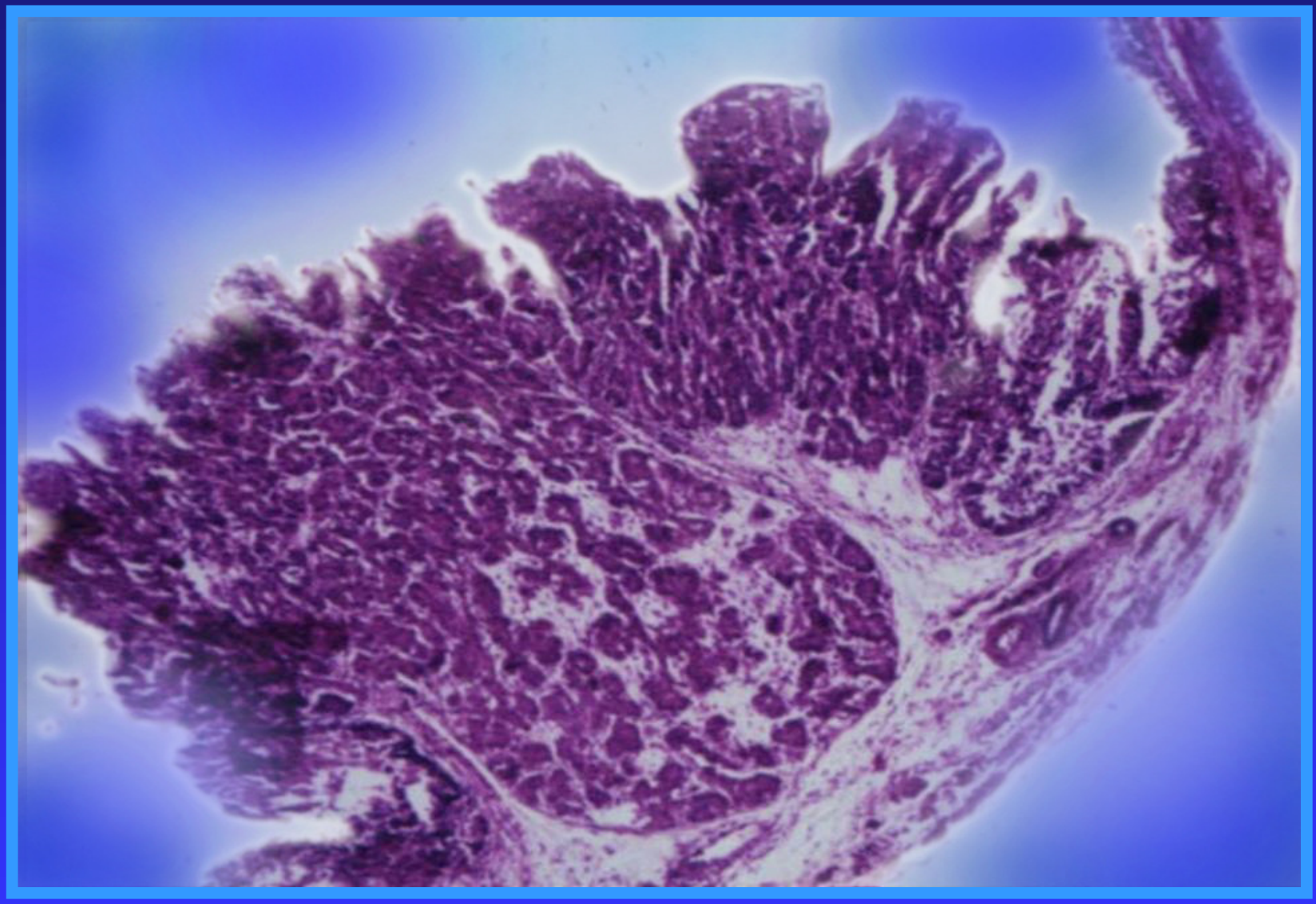
1970's

- multiple claims of success, but controlled trials fail to confirm efficacy in advanced disease, but...

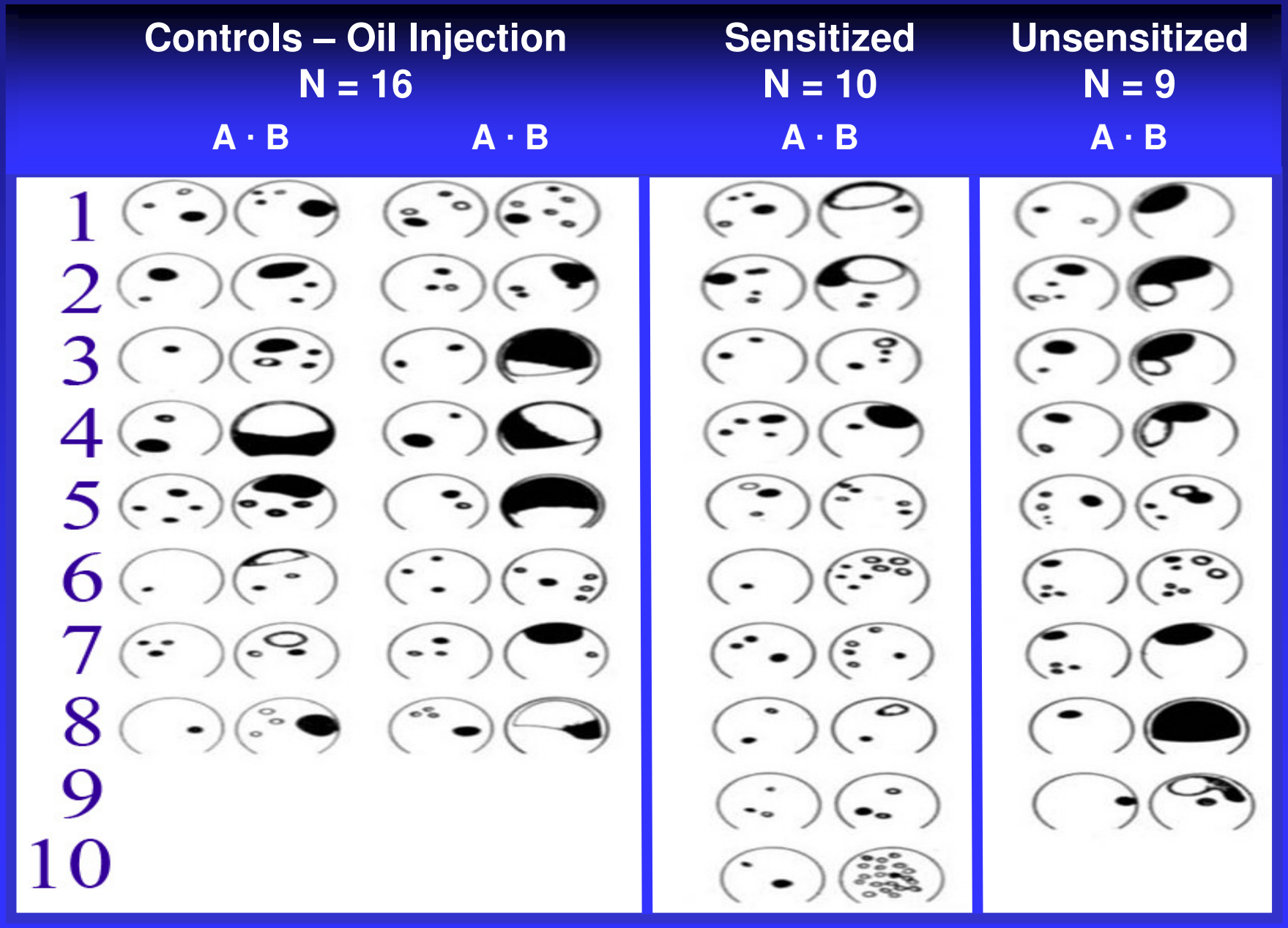
1976

- Morton- 91% CR with BCG injected melanoma nodules





Intralesional BCG Cell Wall Injections



BCG in Bladder Cancer

1976

- Morales- 12 fold reduction in recurrence in nine bladder cancer patients

1977

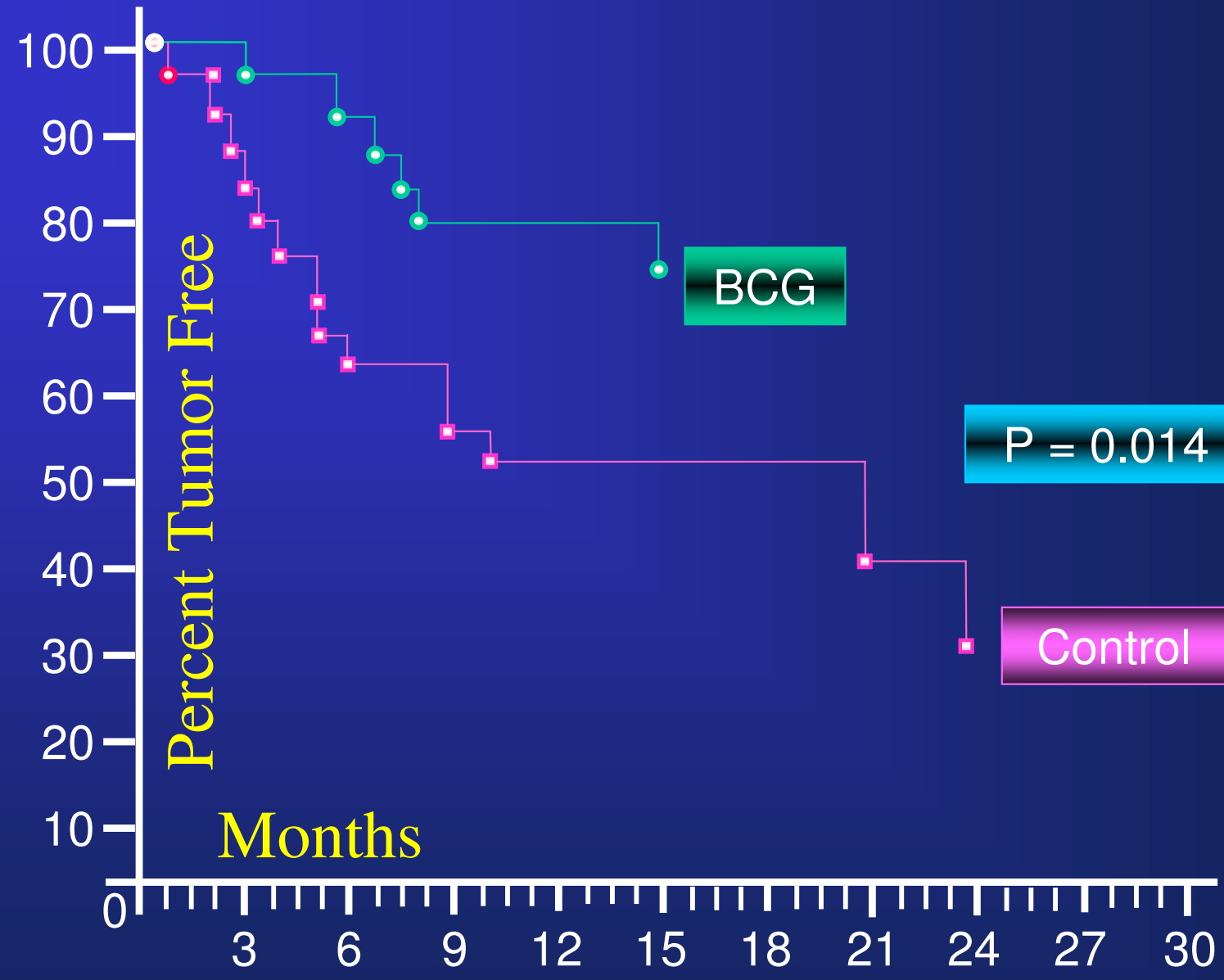
- Lamm reports success in controlled animal studies of bladder cancer

1980

- Lamm reports successful randomized clinical trial

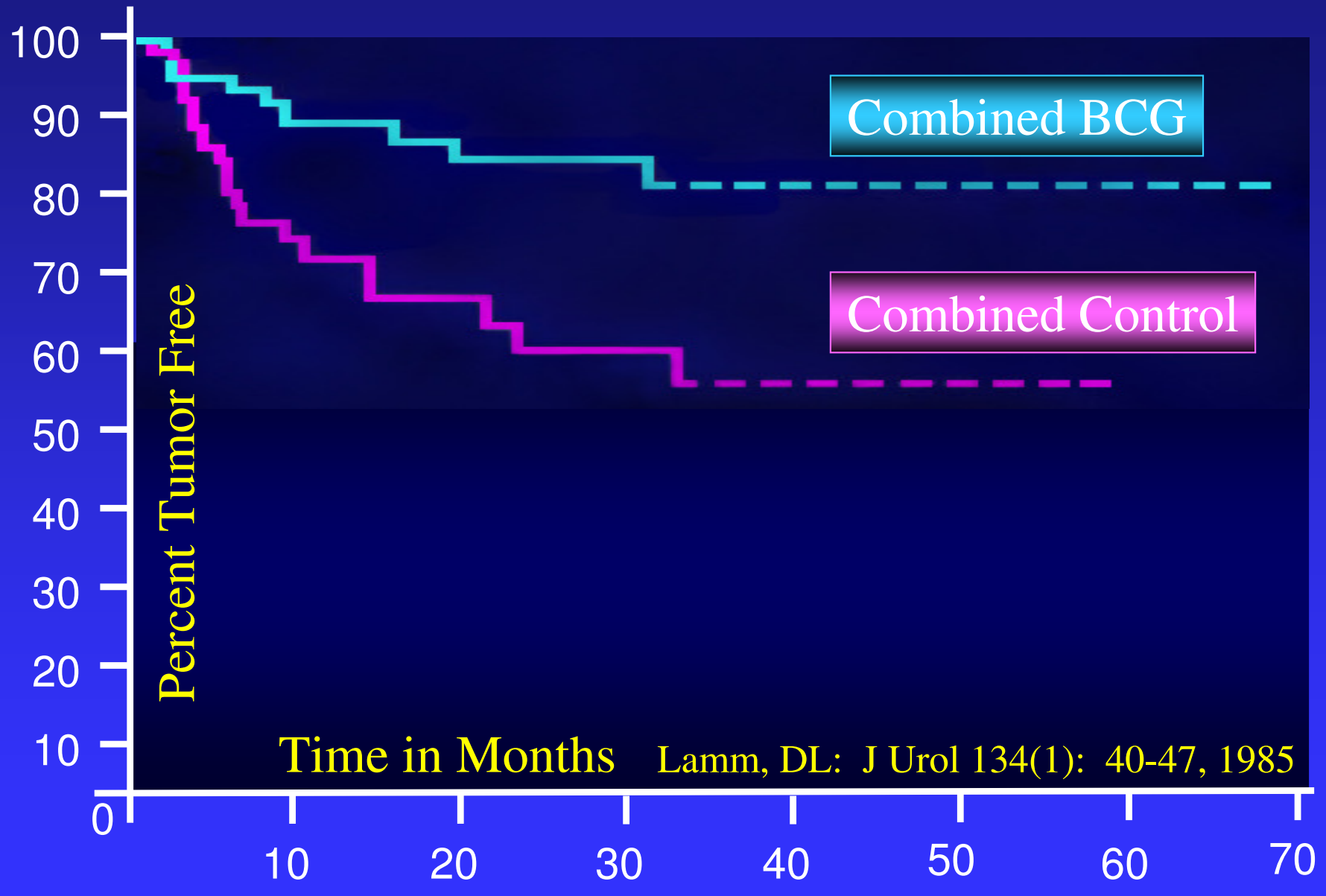
80's-90's

- Multiple comparison studies show BCG to be superior to chemotherapy

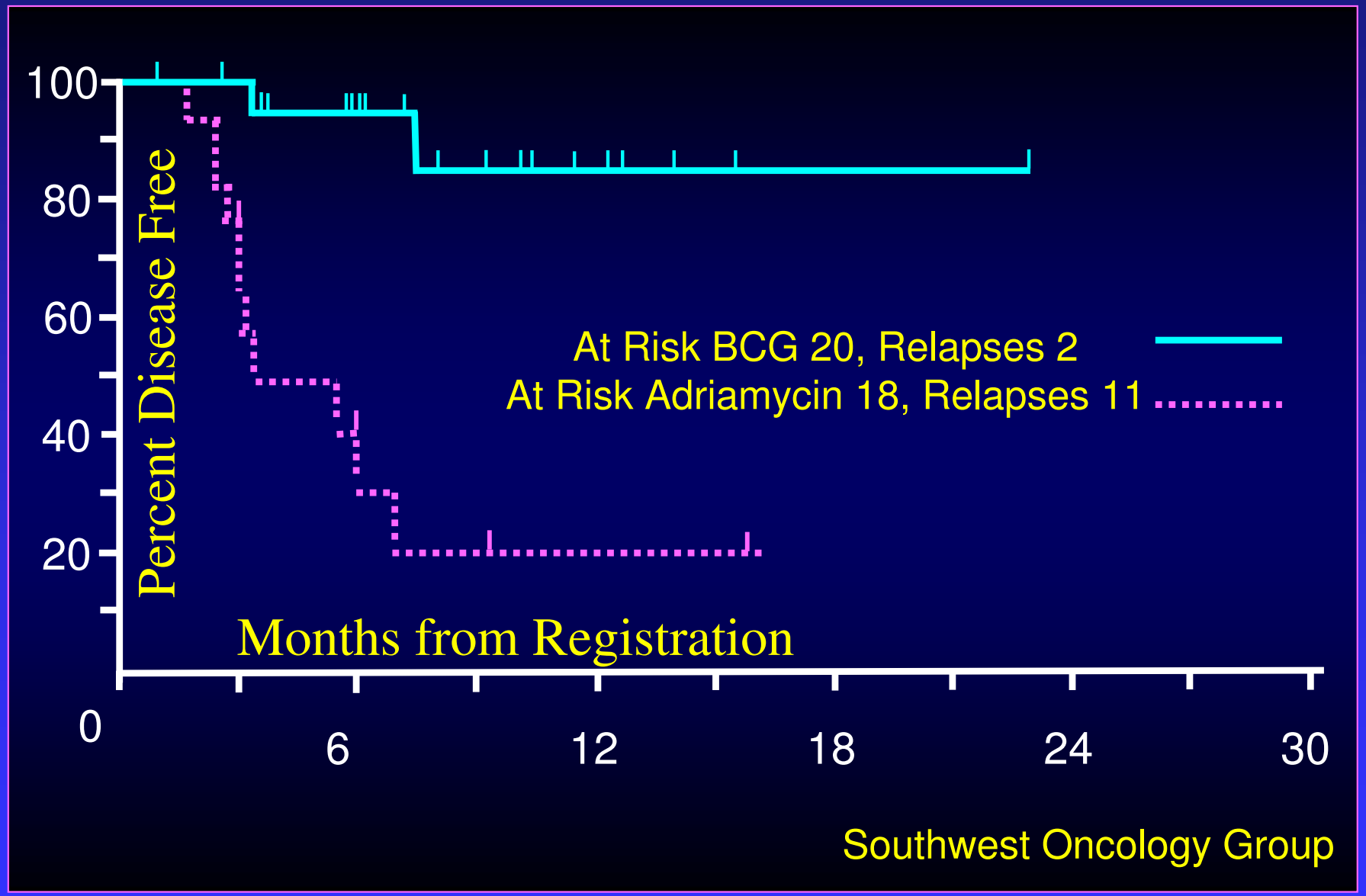


Lamm, DL: J Urol 124(1): 38-40, 1980

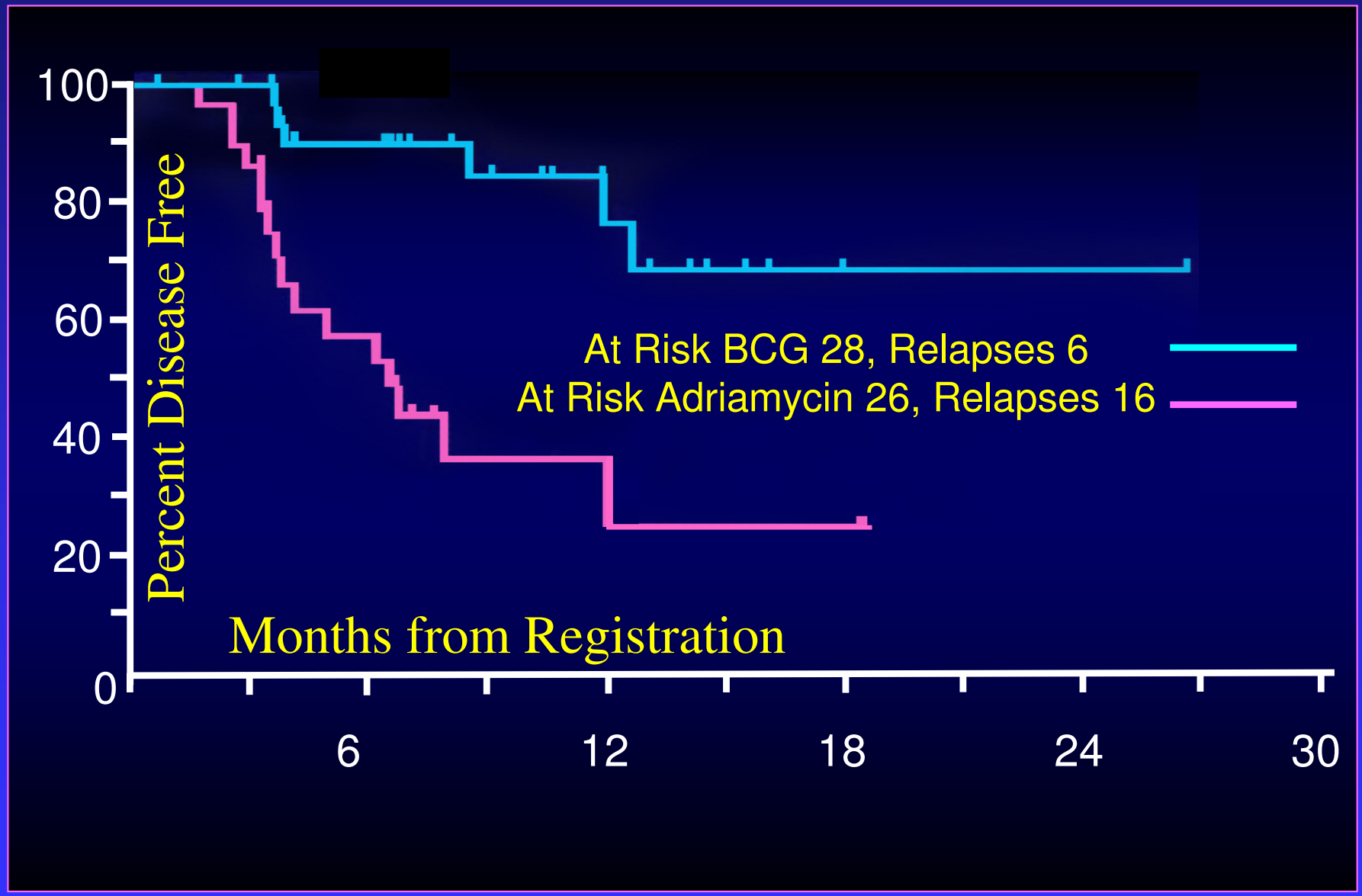
Tumor Recurrence



Disease Free Interval for Patients Without CIS and With Prior Chemotherapy – Protocol 8216



Southwest Oncology Group – Disease Free Interval for Patients Without CIS – Protocol 8216



Progress in Bladder Cancer

- Incidence up from
  - 14.6/100,000 in 1973 to 16.5 in 1997
    (adjusted to 1970 population)
- Mortality down: 4.2/100,000 in 1973 to 3.2 in 1997
  - 5 yr survival 53% in 1950, 82% in 1997
- One of only 5 cancers with *increased* incidence and reduced mortality

Testis	- 5.1
Bladder	- 1.3
Breast	- .3
Ovary	- .5
Thyroid	- 1.1

Seer, 2000

Risk Factors in Superficial Bladder Cancer

Recurrence

- 51% for solitary
- 91% multiple
- As low as 20% @ 5 years if 3 mo. cysto clear

Progression

- 4% for Ta, 30% for T1
- 2% for G1,Ta
- 48% for G3,T1

Mortality

- 6% G1, 21% G3
- CIS: 52% progression T2 or higher if untreated
- T2(+): 45% 5yr survival with cystectomy

Risk Groups Improve Treatment Selection

- Low Risk: G1,Ta solitary tumor with no recurrence at 3 months
- Intermediate Risk: Multiple or recurrent G1,Ta; G2,Ta
- High Risk: Any G3, Lamina propria invasion (T1), CIS, or 3 month recurrence

Mechanisms of Tumor Recurrence

- Implantation at the time of tumor resection
- Incomplete resection
- Stimulation by growth factors induced by surgery and the healing process
- Growth of transformed cells or CIS
- Continued induction and promotion due to continued carcinogen exposure

Principles of Intravesical Chemotherapy

- Direct contact with cancer cells is required
- Tumor kill is proportional to duration of exposure and drug concentration
- Optimal response occurs with treatment within 6 hours of tumor resection
- Significant improvement with continued treatment or maintenance not reported
- Low-grade tumors respond best

Thiotepa: Controlled Studies

Author	N	Control	Thio	% Δ	P
Burnand	51	97%	58%	39%	0.001*
Byar	86	60%	47%	13%	0.016
Nocks	42	64%	65%	-1%	NS
Asahi	134	41%	40%	1%	NS
Schulman	209	69%	59%	10%	NS
Koontz	93	66%	39%	27%	0.02
Zincke	58	71%	30%	41%	0.002*
Prout	90	76%	64%	12%	0.05
MRC	367	37%	40%	-3%	NS
Netto	34	80%	43%	37%	NS
Hirao	93	46%	15%	31%	.002
Total	**1257**	**60.6%**	**44%**	**16.6%**	

Single Immediate Post op Chemotherapy Reduces Tumor Recurrence in Ta,T1 TCC: Meta analysis of Randomized Trials

- 7 trials, 1476 patients, median follow 3.4 years (max 14.5)
- Recurrence: reduced from 362/748 (48.4%) with TUR alone to 267/728 (36.7%) with one postoperative dose epirubicin, MMC, thiotepa or pirarubicin
- 39% reduction in the odds of recurrence with chemotherapy (OR = 0.61, $p < 0.0001$)
- Both single (OR = 0.61) and multiple tumors (OR = 0.44) benefited
- 65.2% with multiple tumors recurred vs. 35.8% with single tumors
- One instillation may be insufficient with multiple tumors

Sylvester R: J Urol abstr. 270, 2004

Mitomycin C: Controlled Studies

Author	N	C	MMC	% Δ	P
Huland	79	52%	10%	42%	0.01
Niijima	278	62%	57%	5%	NS
Kim	43	82%	81%	1%	NS
Tolley	452	60%	41%	19%	0.0002
Krege	234	46%	27%	19%	0.04
Akaza	298	33%	24%	9%	NS
Total:	1384	51.5%	37.6%	13.9%	

Summary of Controlled Chemotherapy Trials

Agent	Series/N	% Δ	(range)	P<0.05
Thiotepa	1257/11	16.6%	(-3-41)	6/11
Doxorubicin	1751/8	16.2%	(5-39)	4/8
Mitomycin	1384/6	13.9%	(1-42)	3/6
Ethoglucid	226/1	20.0%	(NA)	1/1
Epirubicin	985/6	19.6%	(9-26)	3/6
Total:	2297/32	17%	(-3-42)	17/32

Controlled BCG Trials

Author	No.	NoRx	BCG	Ben.	P
Lamm ‘85	57	52%	20%	32%	<.001
Herr ’85	86	95%	42%	53%	<.001
Yamamoto ‘90	44	67%	17%	50%	<.0.05
Pagano ’91	133	83%	26%	57%	<.001
Mekelos ’93	94	59%	32%	27%	<0.02
Krege ’96	224	48%	29%	24%	<0.05
Kolodziej ’02	155	55%	19%	36%	<.001
Total:	798	66%	26%	40%	

Meta-Analysis of BCG vs. TUR Alone

Shelly et al. Cochrane Group BJU Int 2001, 88:209

- 26 publications reviewed
- 6 acceptable trials with 585 patients
- Mean log hazard ratio for recurrence -.83, $P<0.001$
- 56% reduction in hazard attributable to BCG
- Manageable toxicity: cystitis 67%, hematuria 23%, fever 25%, frequency 71%
- Conclusion: BCG provides significantly better prophylaxis of tumor recurrence in Ta, T1 TCC

Randomized BCG vs. Chemotherapy Studies

Thiotepa					
BCG	Rec	Chemo	Adv.	P value	Author
0	vs	47%	+47	<.01	Brosman ‘82
7%	vs	43%	+35	<.01	Netto ‘83
13%	vs	36%	+26	<0.05	Martinez ‘90
Doxorubicin					
53%	vs	78%	+21	<.02	Lamm ‘91
13%	vs	43%	+30	<.01	Martinez ‘90
24%	vs	42%	+18	<.05	Tanaka ‘94
Epirubicin					
33%	vs	47%	+14	<.0001	Vd Meijden ‘01

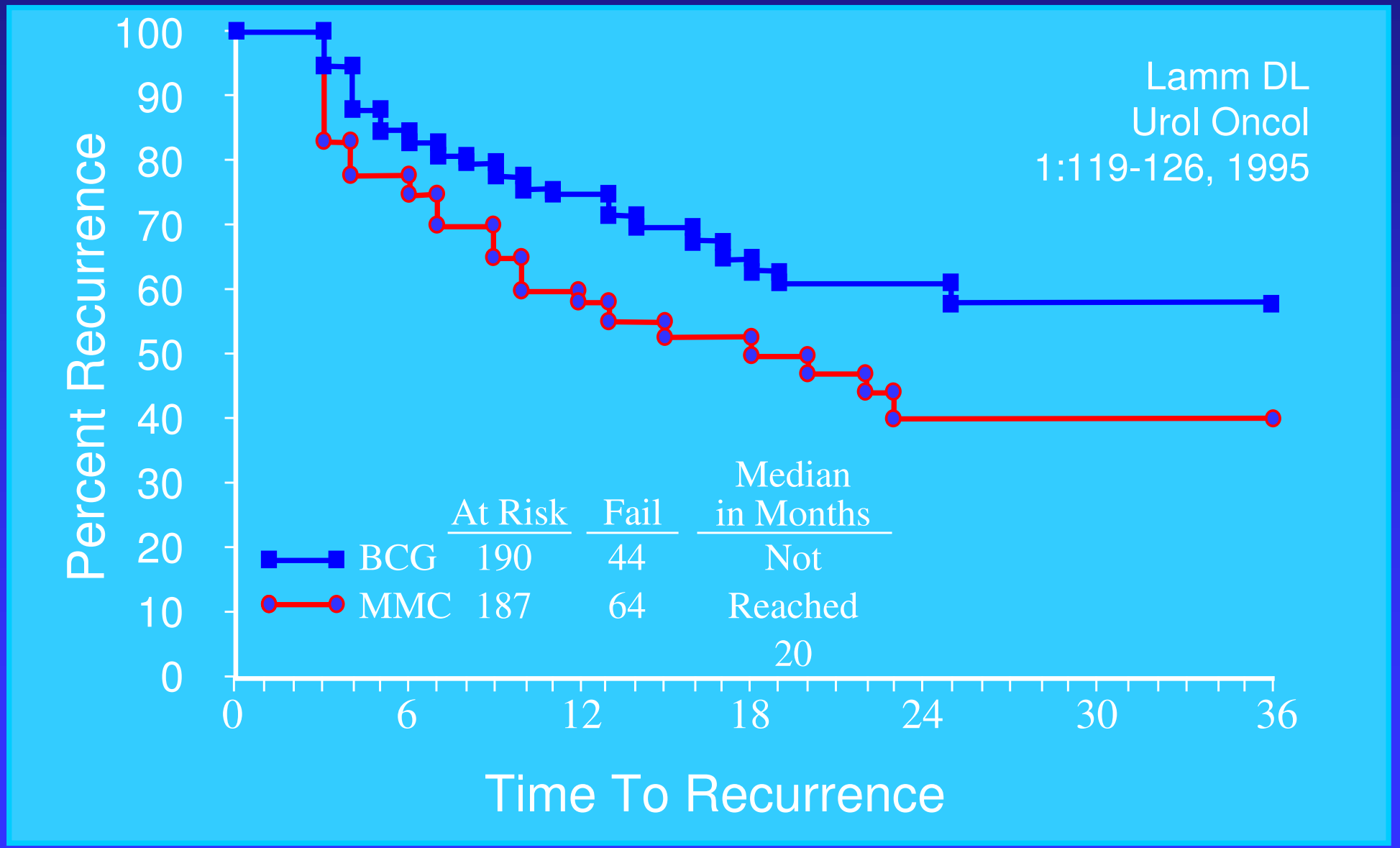
Randomized BCG vs. MMC Studies

BCG	Rec.	MMC	Δ BDG	P Value	Author/Year
4%	vs	34%	+30	<.01*	Pagano '87
28%	vs	62%	+34	<.001*	Finnblad '89
61%	vs	80%	+19	NS	Lee '92
47%	vs	42%	-5	NS	Witjes '94
64%	vs	42%	-21		Vegt '95
46%	vs	43%	-3	NS	Vegt '95
43%	vs	56%	+9	<.01*	SWOG '96
51%	vs	66%	+15	<.01*	Malmstyr. '96
24%	vs	29%	+5	NS	Krege '96
38%	vs	62%	+24	<.001*	Ayed '98
32%	vs	54%	+22	<.001*	Milan '00
14%	vs	26%	+13	<.01	Nogueira '01

36.7% of 781 vs 53.8% of 771 (+17%) in maintenance BCG studies.

6/6 maintenance BCG studies significant vs 1/5 non-maint.

BCG Versus Mitomycin-C (SWOG 8795)



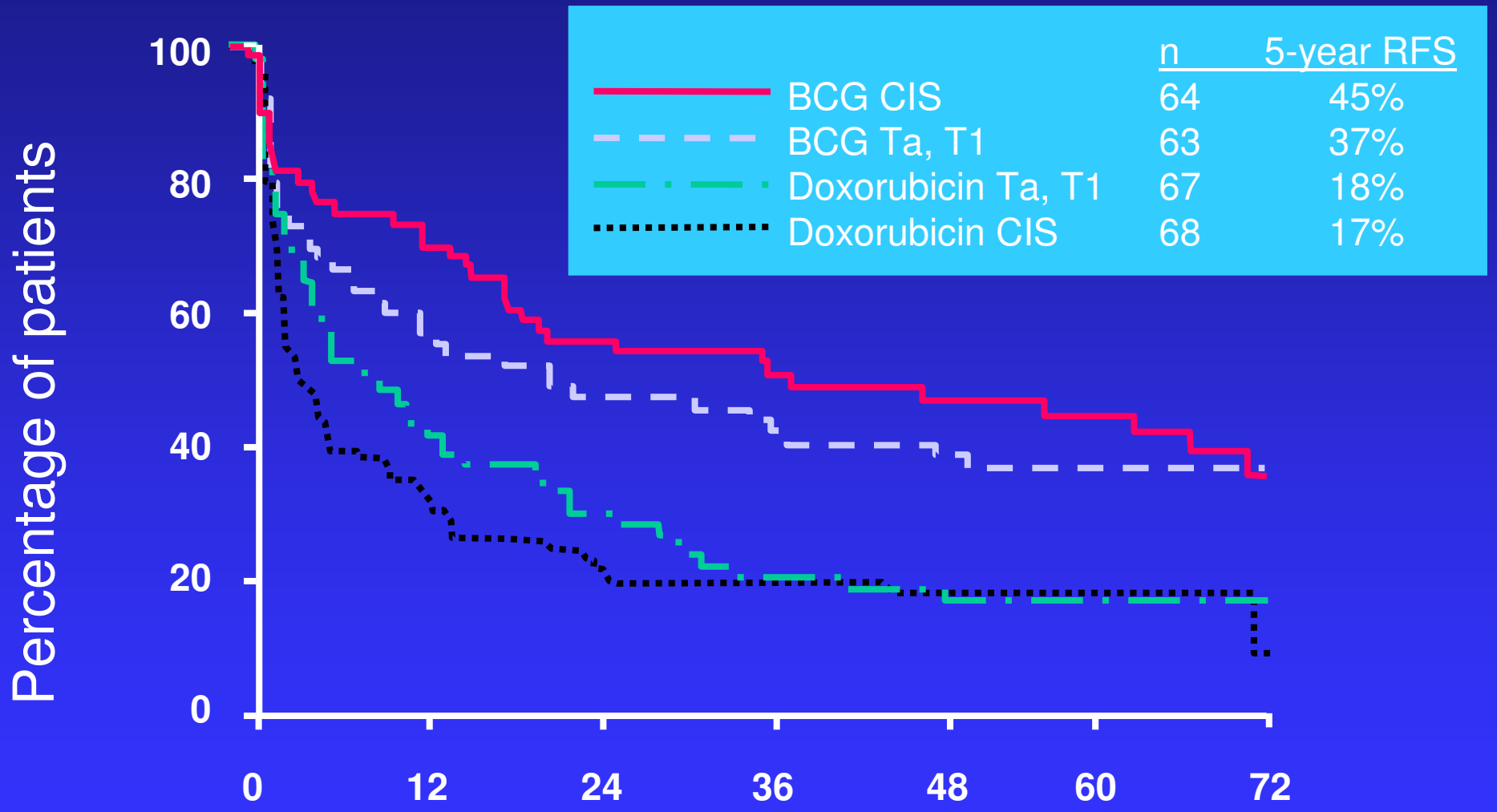
Intravesical BCG is superior to mitomycin C in reducing tumour recurrence in high-risk superficial bladder cancer: a meta-analysis of randomized trials. Shelley et al. (2004) BJU Int. 93:485-90

- "This is the highest level of evidence-based medicine and the results presented here suggest that intravesical BCG is superior to mitomcycin C."
- "A subgroup analysis of 3 trials that included only high-risk Ta and T1 patients indicated no heterogeneity (P-0.25) and a LHR for recurrence of -0.371 (0.012). With MMC used as the control in the meta-analysis, a negative ratio is in favour of BCG and, in this case, was highly significant (P<0.001)."

Optimal Intravesical Chemotherapy

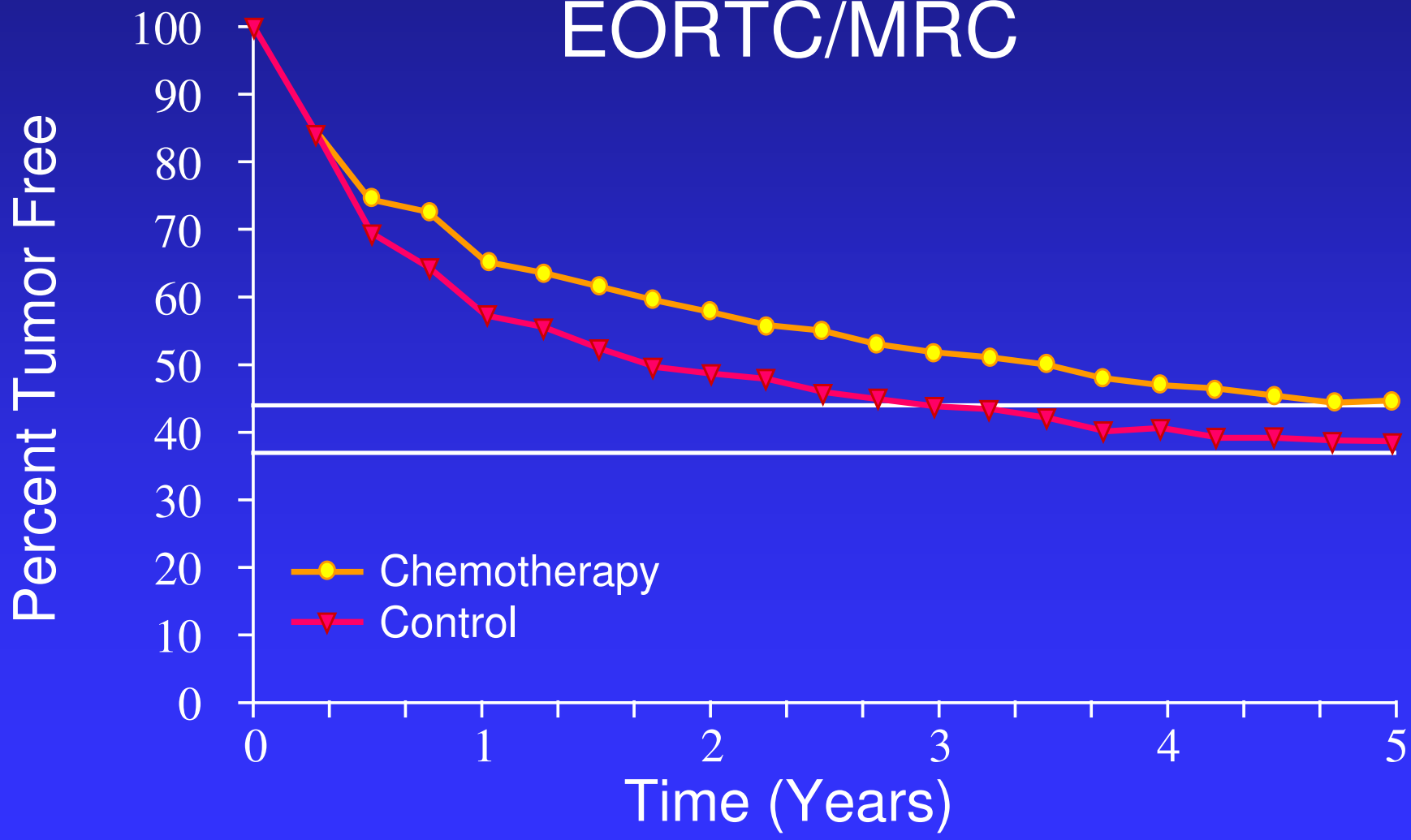
- Immediate postoperative treatment is best, confirmed by meta-analysis (Sylvester, 2004)
- *Concentration* is more important than dose: 40mg MMC/20ml water, 30mg thiotepa/15cc, 50mg Adra/25cc all for 30 minutes within 6 hours post op
- MMC: 40mg/20ml, dehydration, ultrasound confirmed bladder drainage and 1.3g bicarb. HS, AM and at time of instillation doubles protection from recurrence (Au, JNCI, 2001)

BCG Versus Doxorubicin: Time Without Treatment Failure



Lamm DL: *N Engl J Med*. 1991;325:1205

5 Year Tumor Recurrence Curves With Chemotherapy vs Control



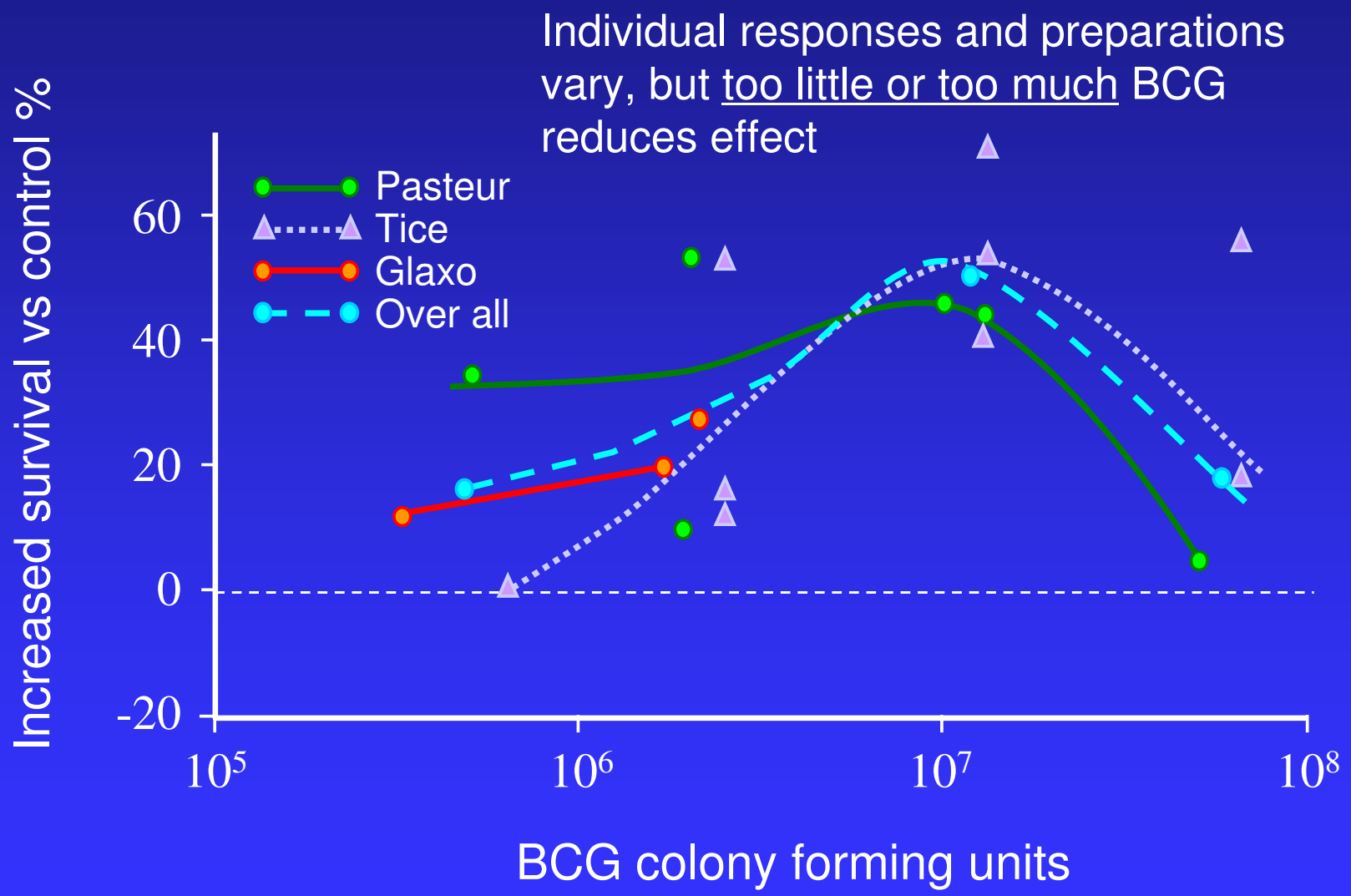
BCG vs Chemo For CIS: Meta-Analysis Sylvester: J Urol. 174:86, 2005

- 9 randomized trials including 700 pts. with CIS
- Chemo: MMC, Epi, Adria, or sequential MMC/Adria
- BCG: 68% CR vs Chemo: CR 52%; P=0.0002
- 3.6 year follow: 47% BCG vs 26% Chemo NED
- 26% reduction in disease progression with BCG
- "BCG reduces the risk of short and long-term treatment failure compared with chemotherapy… agent of choice in the treatment of CIS."

Principles of BCG Immunotherapy

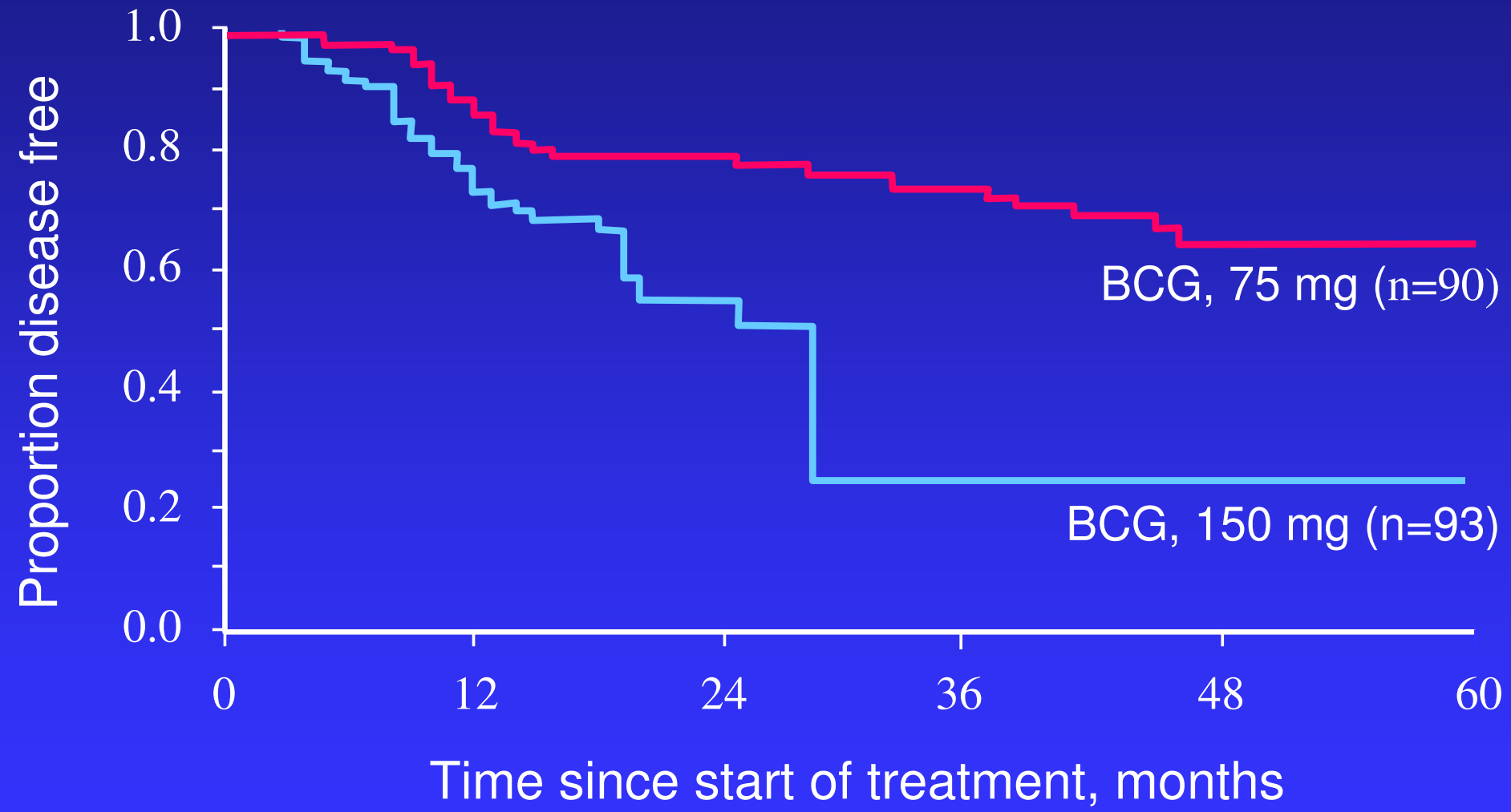
- *Minimize* tumor burden (10^3 cells, mouse)
- *Juxtapose* BCG and tumor cells
- Use sufficient but not excess BCG (Dose-Response curve is Bell-shaped). Excess BCG (eg repeated 6 week courses) *suppresses* the immune response
- Initial immune stimulation peaks at 6 weeks, subsequently at 3 weeks
- Immune stimulation wanes with time
- TH1 immune competent host & antigenic tumor

Dose-Response Curve to BCG (in mice)



Lamm DL, et al. *J Urol*. 1982; 128: 1104-1108

Low-Dose Versus High-Dose BCG



* Pasteur strain, Pagano F, et al. *Eur Urol*. 1995; 27 (suppl 1): 19-22.

Why Maintenance BCG?

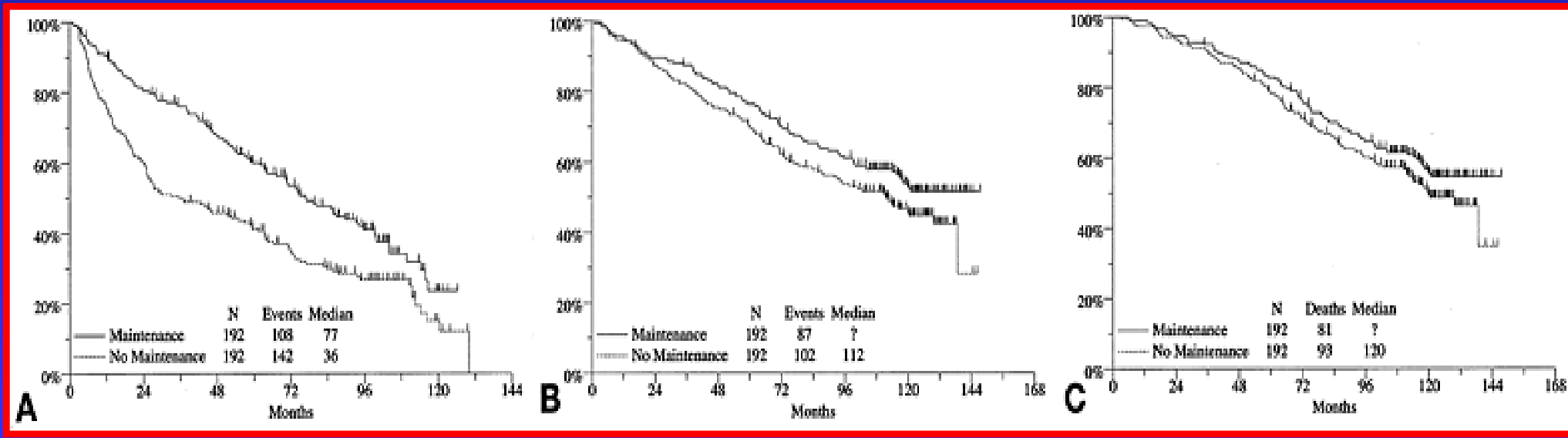
- The risk of tumor recurrence is lifelong
- The immune stimulation and protection from tumor recurrence induced by BCG wanes with time

Three Week Maintenance BCG
SWOG 8795: 385 Evaluable, NED

Recurrence -free Survival

Worsening -free Survival

Survival



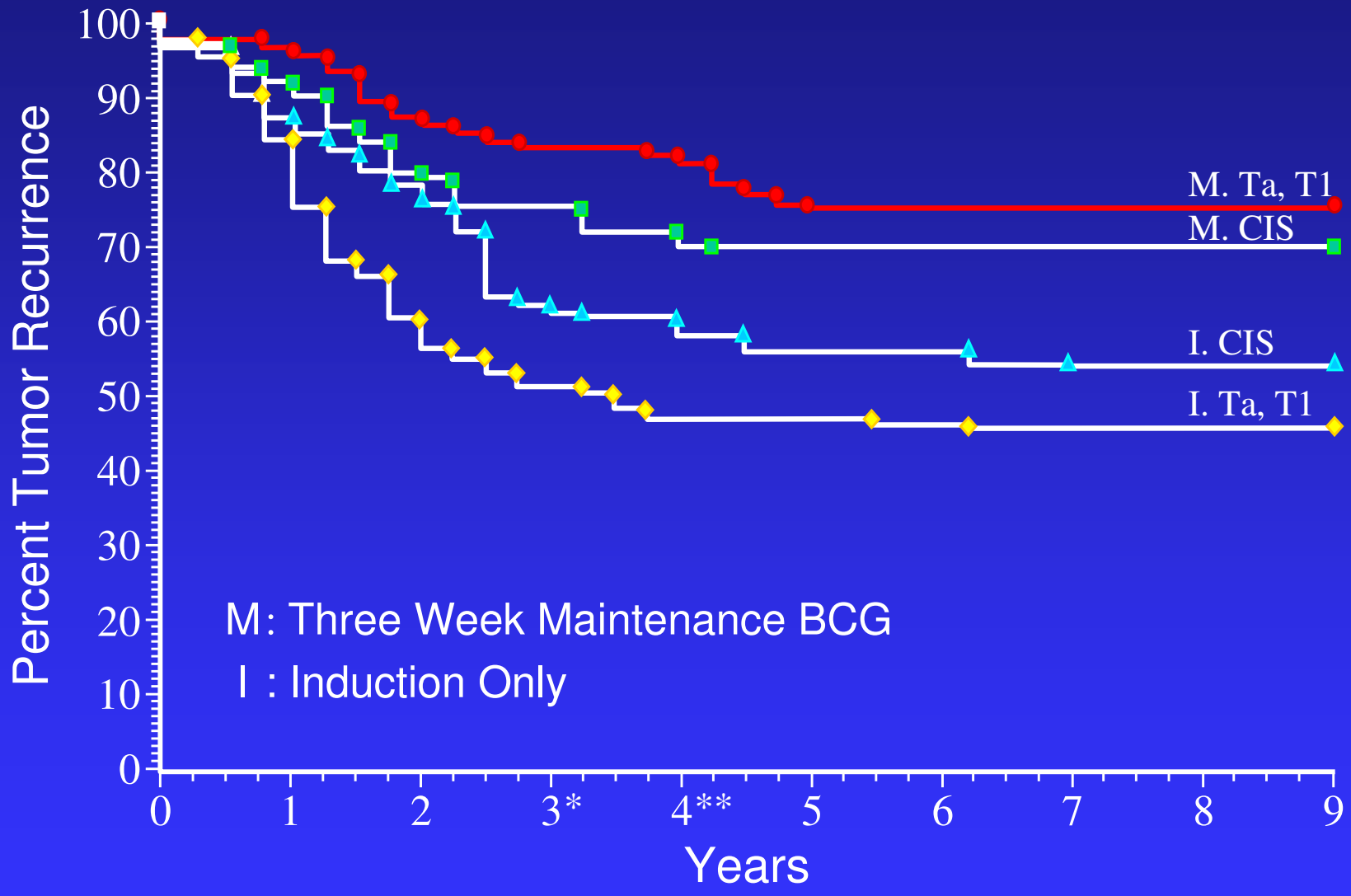
$p < 0.0001$

$p = 0.04$

$p = 0.08$

Lamm DL et al, J Urol 163, 1124, 2000

Figure 1



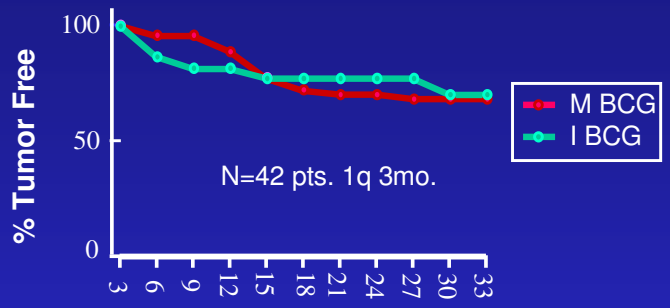
* Completion of Therapy

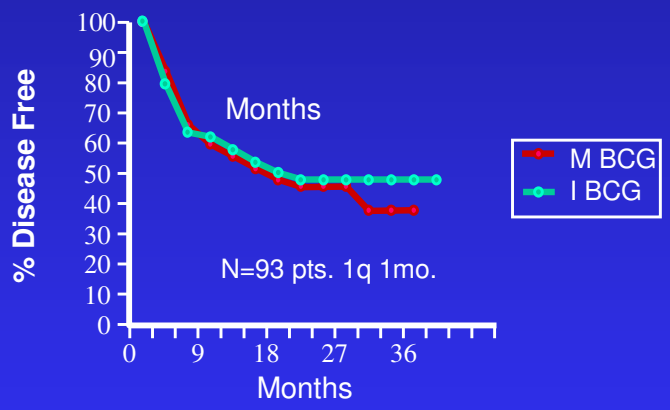
** Apparent Increase in Rate of Recurrence One Year After Completion of Maintenance

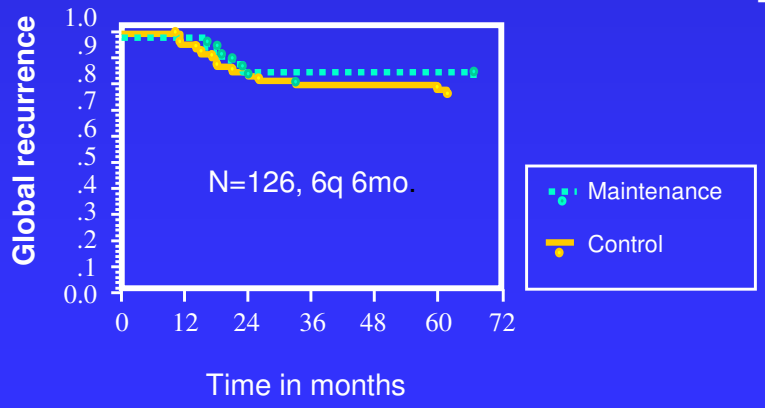
Results

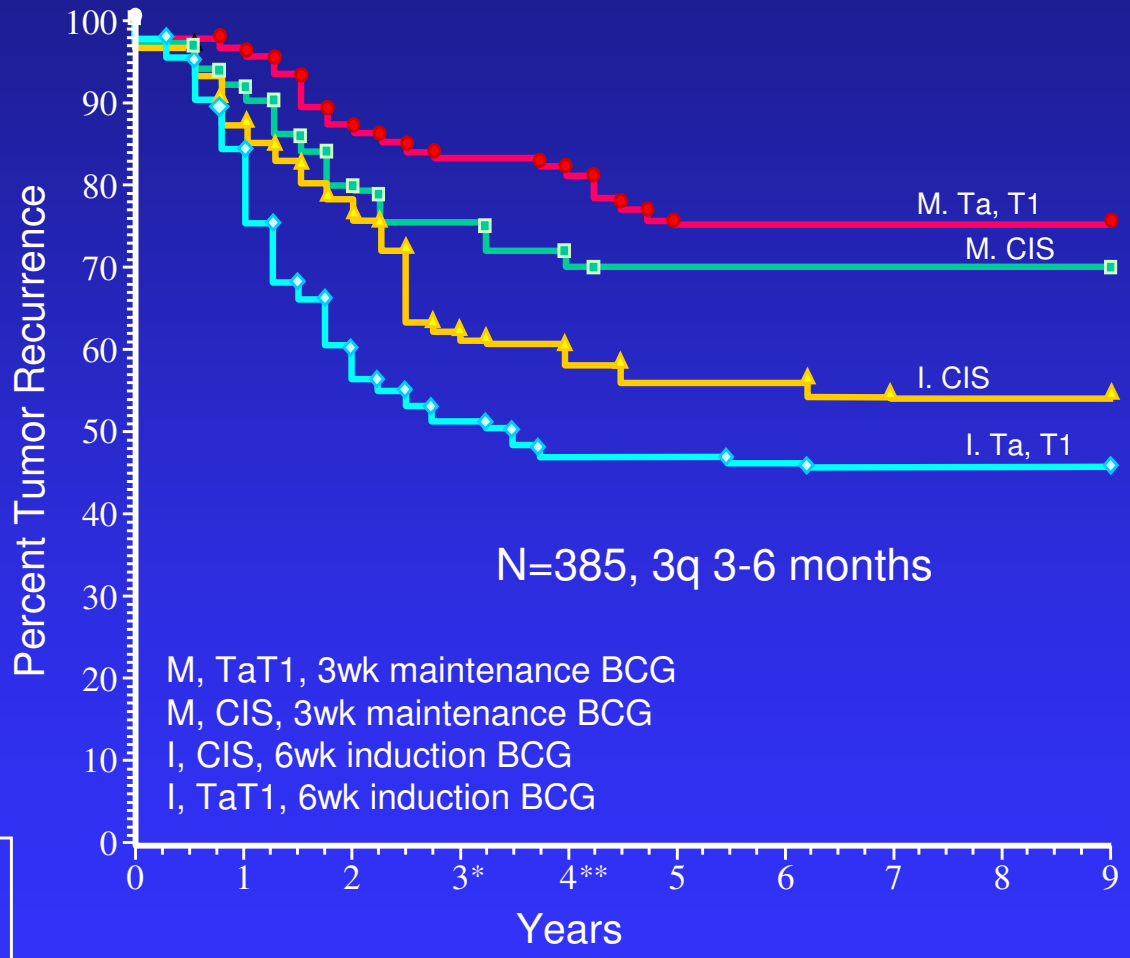
- With 10 year follow-up, recurrence reduced from 52% to 25% (P<0.0001)
- Recurrence-free survival increased from 30% to 48% (P<0.0001)
- Worsening-free survival increased from 52% to 60% (P<0.04)
- Overall survival increased from 51.5% to 57.8% (P=0.08, NS)

BCG Maintenance: Not Created Equal



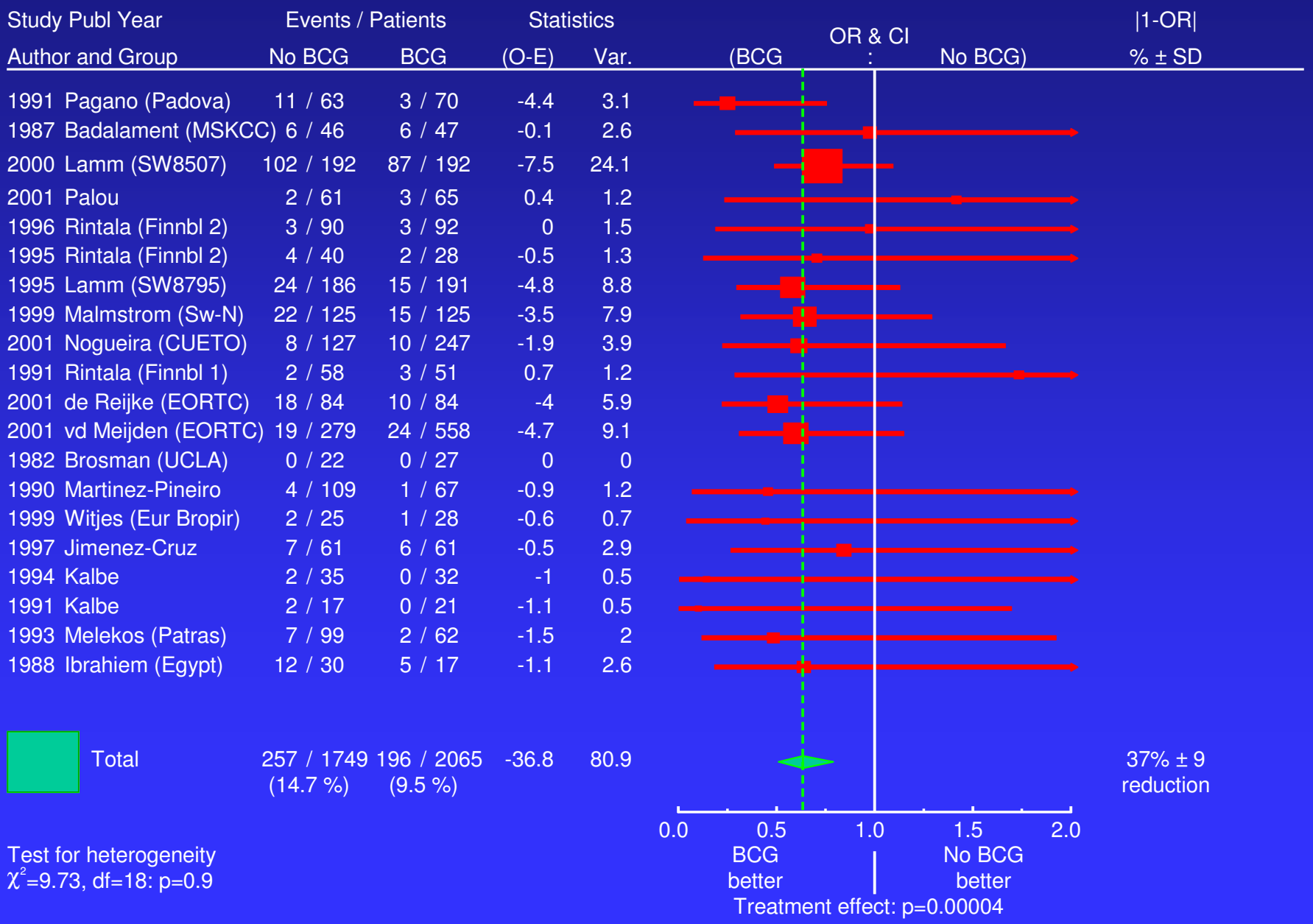






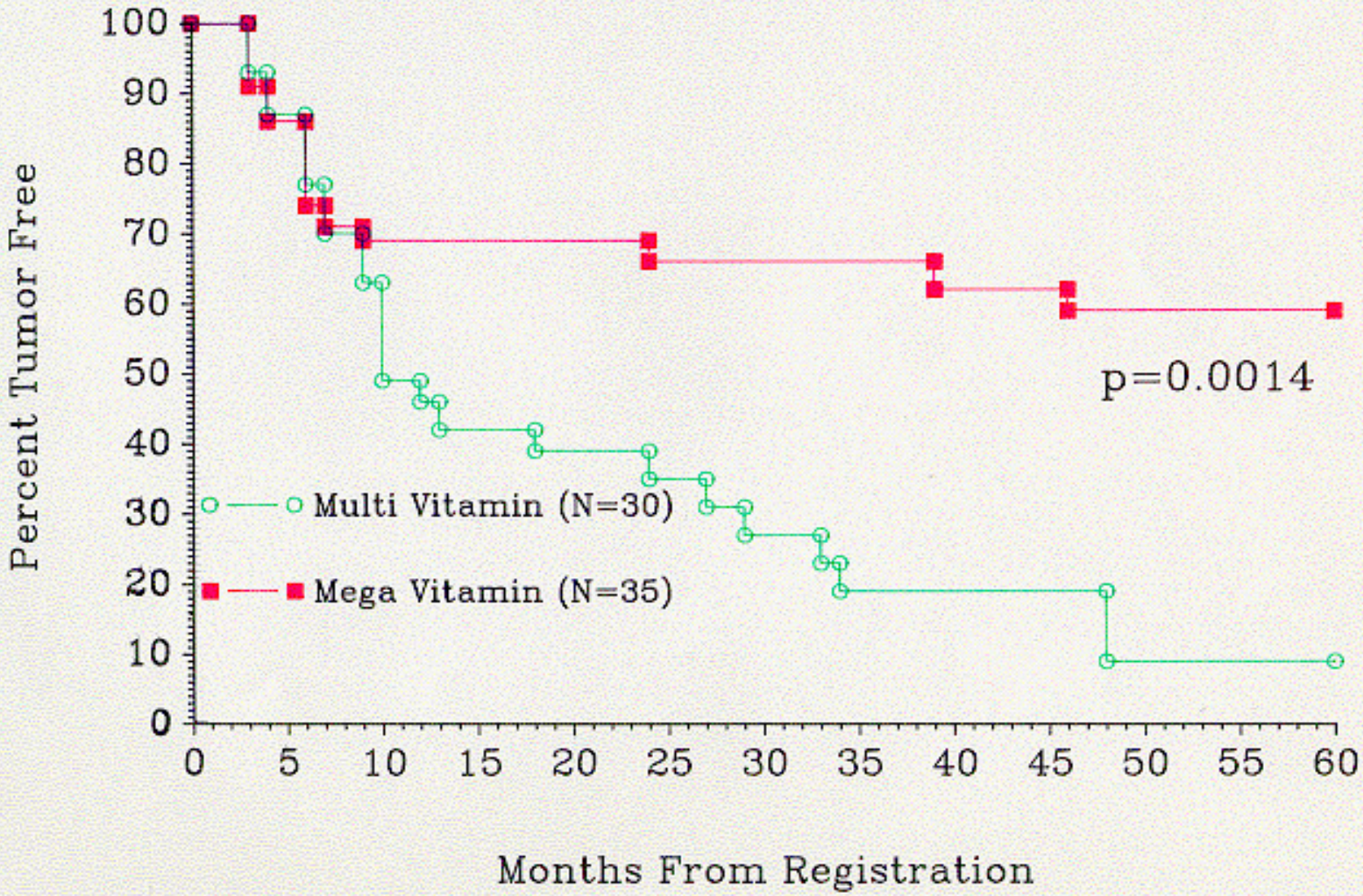
* Completion of Therapy
* Apparent Increase in Rate of Recurrence
** One Year After Completion of Maintenance

Progression All Studies With Maintenance



Kaplan Meier Estimate of 5 Year Tumor Free Rate

In Patients Receiving Vitamin Supplement and BCG Therapy For Bladder Carcinoma



Natural and Chemotherapy Treated History of T1, G3, TCC

Author	No.	Progr.	Follow-up
Heney ’83	27	48%	36 mo.
Rutt ‘ 85	430	31%	60 mo.
Malmstrom ‘87	7	43%	60 mo.
Jakse ‘87	31	33%	60 mo.
Kaubisch ‘91	18	50%	36 mo.
Mulders ‘94	48	27%	48 mo.
Klan ‘95	17	65%	72 mo.
Holmang ‘97	58	48%	84 mo.
Total:	519	33%	

BCG in Grade 3, Stage T1 TCC

Author	No.	Prog. %	Followup	Author	No.	Prog %	Follow-up
Boccon - Gibod '89	47	12	-	Vicente '96	95	11	46
Dal Bo '90	24	25	22	Lebret '98	35	12	45
Samodi '91	62	0	46	Baniel '98	78	8	56
Cookson '92	86	7	59	Klan '98	109	13	78
Eure '92	30*	7	39	Gohji '99	25	4	63
Pfister '95	26	27	54	Brake '00	44	16	43
Hurle '96	51	14	33	Pansadoro '02	86	14	71
Zhang '96	23	35	45	**Total**	**871**	**12**	
Sereretta '96	50	12	52				

Clinical v. Pathologic Staging Stage T1 TCC

Cystectomy in **101** Clinical State T1 patients
Final Pathologic States

- 70 patients stage pT1 or less:
  - pTO: 19
  - pTIS: 4
  - pTa: 0
  - pT1: **47**

- **31** patients pT2 or greater:
  - pT2: 10
  - pT3a: 2
  - pT3b: 8
  - pT4: 11

Amling, J. Urol, 1991

Understaging of High-Risk Superficial Bladder Cancer

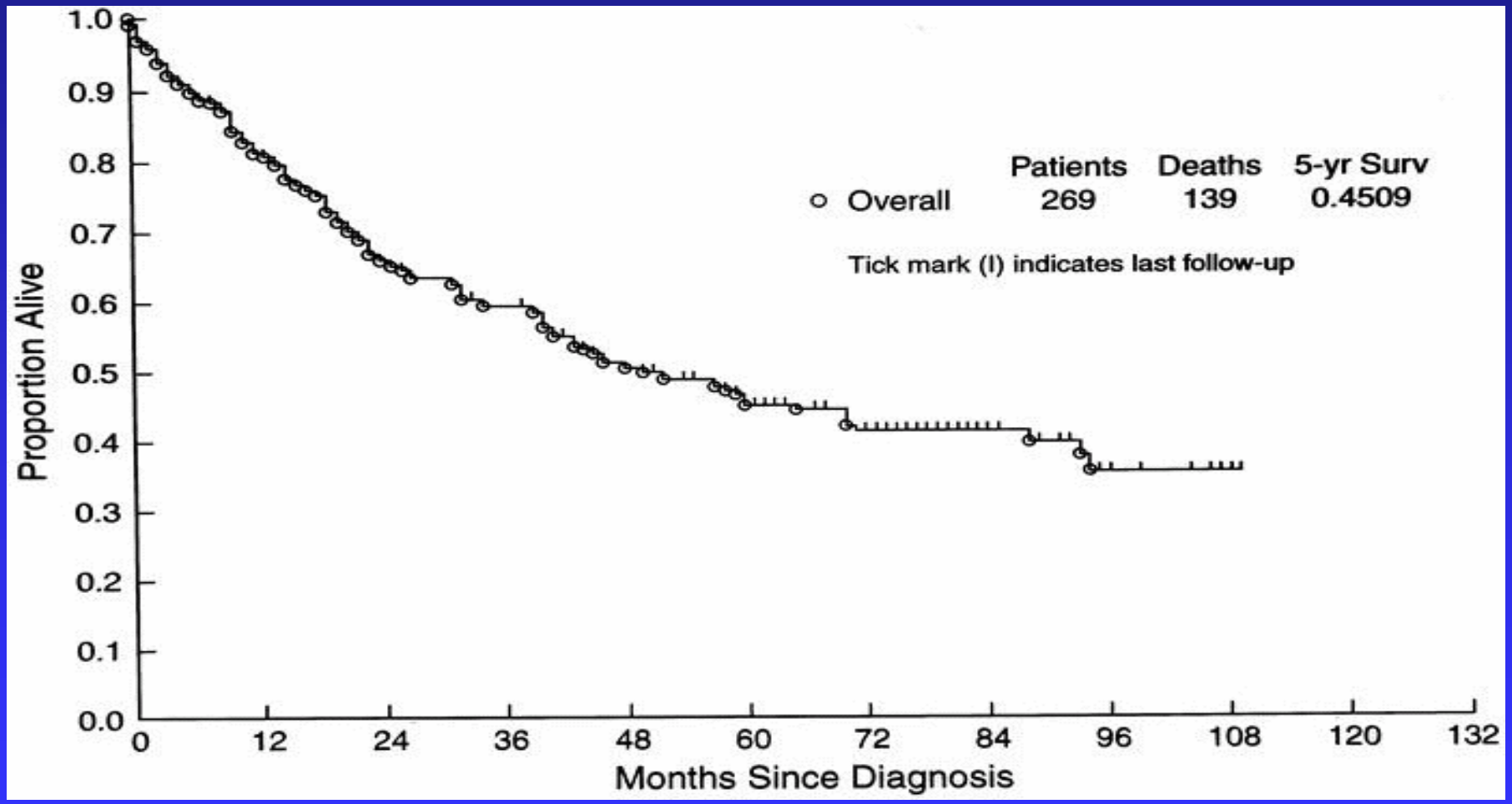
Study		% Understaged
Pagano	(1991)	35%
Amling	(1994)	37%
Soloway	(1994)	36%
Freeman	(1995)	34%
Ghoneim	(1997)	62%
Herr	(1999)	49%
Dutta	(2001)	64%
Overall Average:		45%

Cystectomy is The Gold Standard for Invasive TCC How Good is Gold?

- Pelvic recurrence: 5-30%
- Overall 5 yr survival: 42-60%
- Morbidity and mortality (0.3-6%)

Current Survival with Cystectomy

Dalbagni: J Urol, 165:1111-1116, 2001



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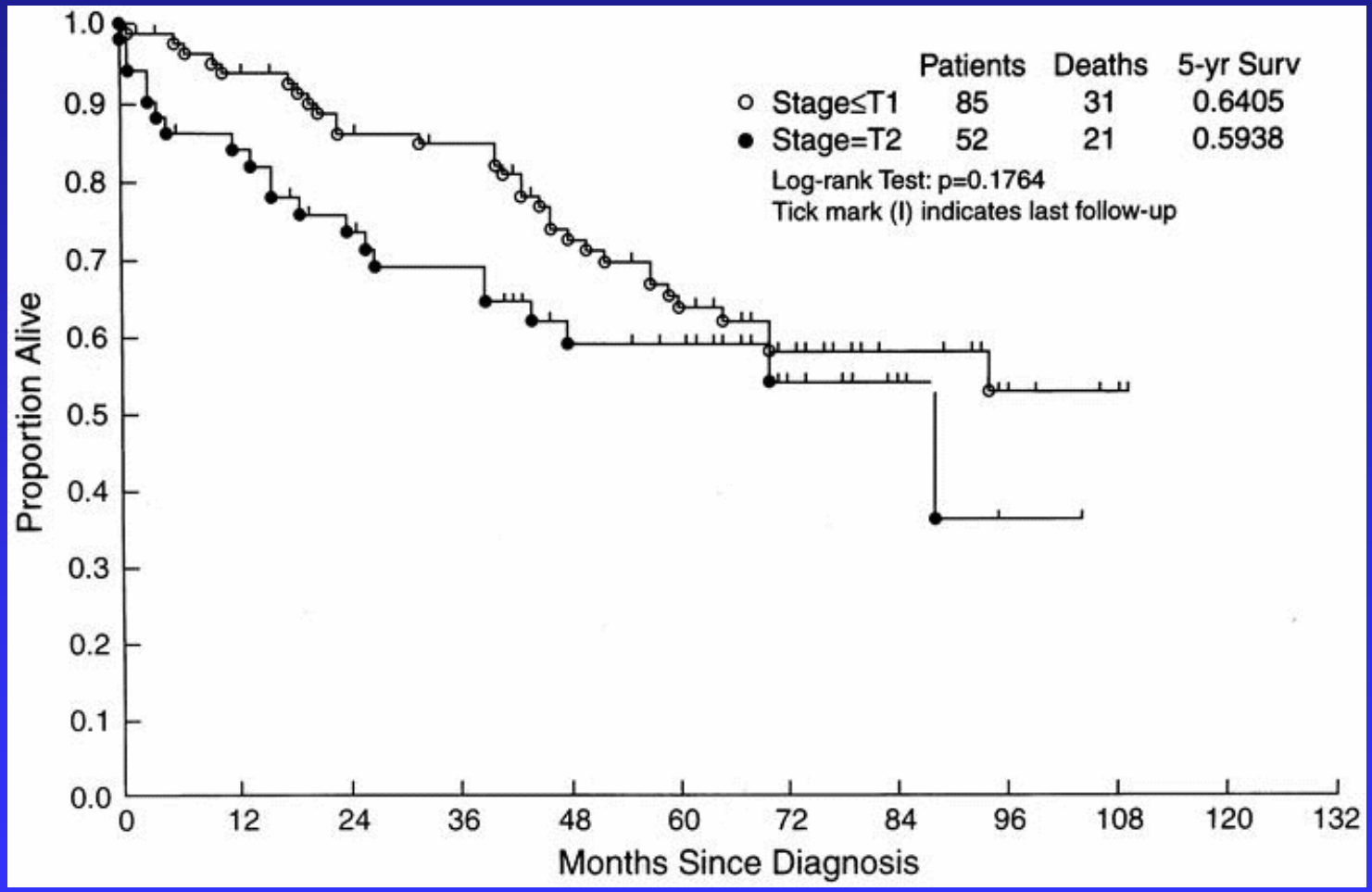


TUR for Muscle Invasive TCC

- Barnes: 40% 5 yr survival when confined to bladder
- Solsona: 59 pts, 75% 10 yr DFS, 80% bladder preservation

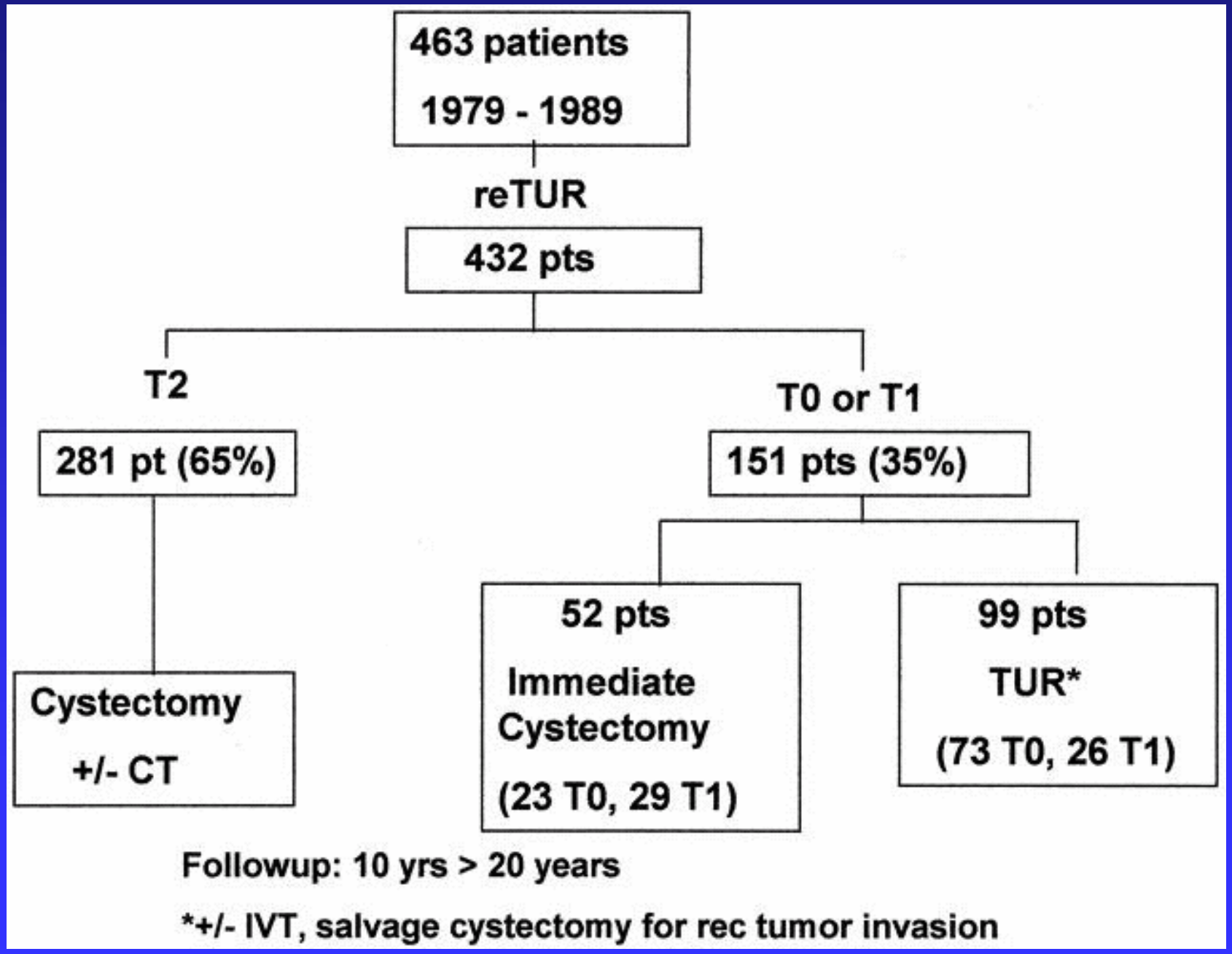
Partial Cystectomy
for Muscle Invasive Bladder Cancer

- 37 patients, 1982-2003 followed for 73 months (6-217).
- 51% had no tumor recurrence.
- 9 (24%) superficial and 9 (24%) invasive or advanced recurrence.
- 6 (16%) died of bladder cancer
- 5 year overall and DSS: 67% and 87%

Kassouf W: J Urol. 2006;175:2058-62 . MD Anderson

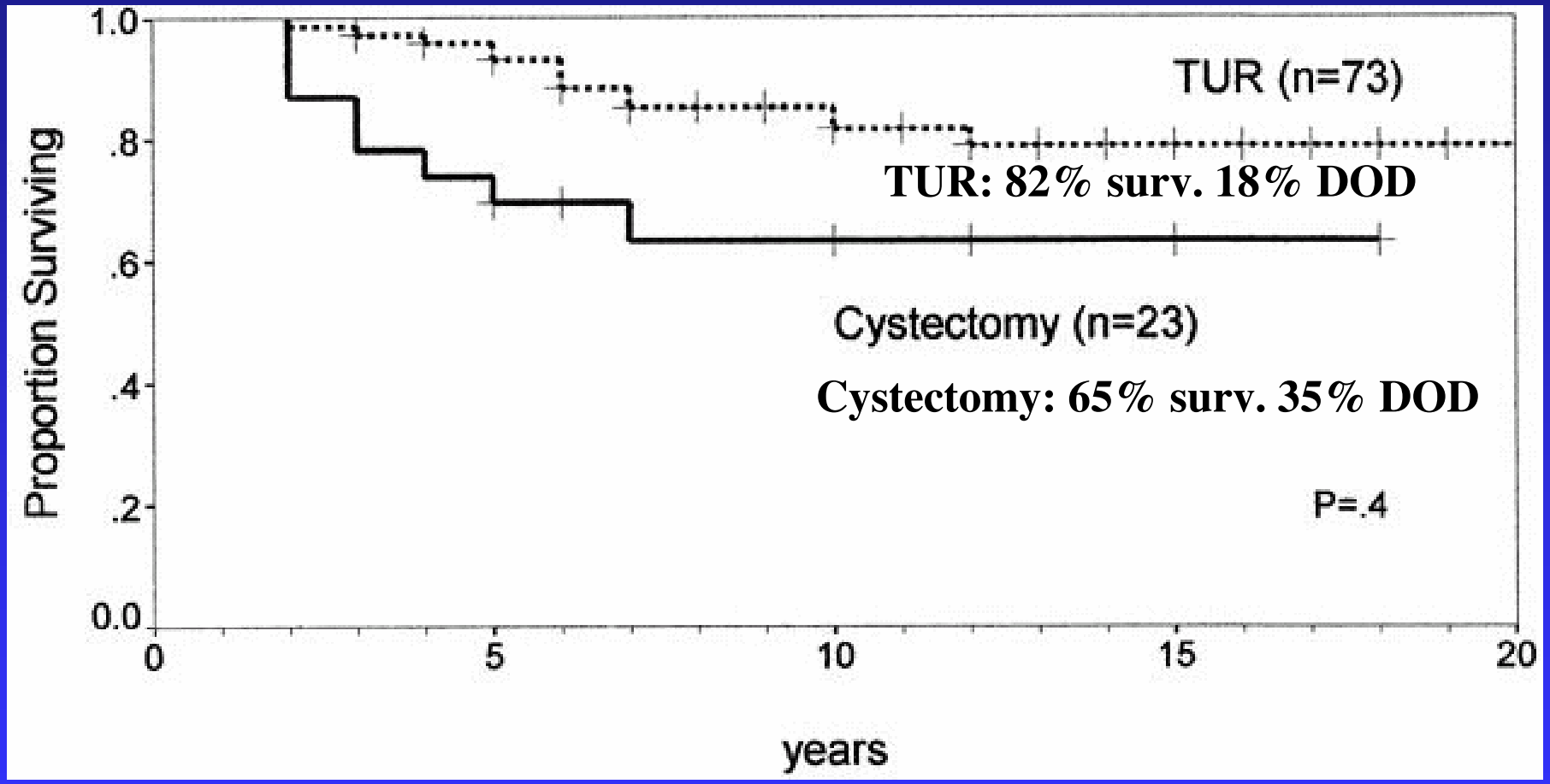
463 Muscle-Invasive TCC Patients

Herr: J Clin Oncol, 19: 89-93, 2001.



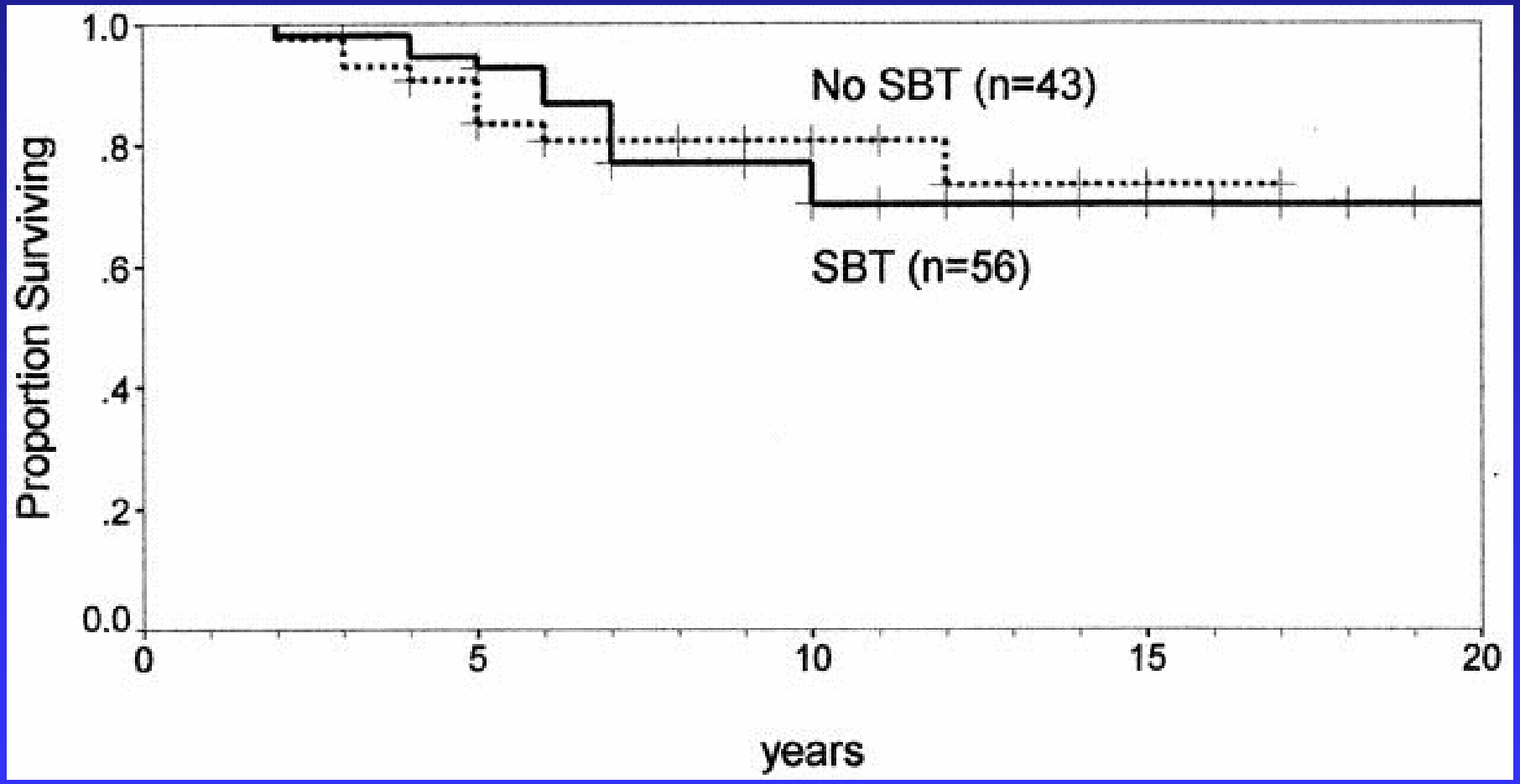
TUR vs. Cystectomy for T2 ⇒T0 TCC

Herr: J Clin Oncol, 19: 89-93, 2001.



151 non-randomized pts, 99 TUR only, 52 immediate cystectomy

Superficial Recurrence: No Effect on Survival
Herr: J Clin Oncol, 19:89-93, 2001.



TUR and BCG in Invasive TCC

Author/yr	N	%NED	Follow
Netto ‘84	10	60%	32 mo
Lamm ‘84	17	41%	24 mo
Pansadoro ‘87	41	24%	18 mo
Rosenbaum ‘96	13	15%	60+mo
Volkmer ‘03	22	46%	60 mo*

69% 5yr survival, P0 2nd TUR

Neo Adjuvant Chemotherapy: Meta Analysis

- 10 randomized clinical trials, 2688 patients
- 13% reduction in bladder cancer death (hazard ratio 0.87, P=0.016)
- 5 yr overall survival increased from 45 to 50%
- No significant benefit for platinum alone

Lancet. 2003;361(9373):1927-34.

Adjuvant Chemotherapy Post Cystectomy or RT: Meta- Analysis

- 491 patients in 6 randomized trials
- 25% reduction in mortality (HR 0.75; 95%: 0.061-0.09, P=0.019)
- Overall **3 yr** survival increased from 45% to 54% with adjuvant chemotherapy

ABC Meta-analysis Collaboration:
Cochrane Database of Systematic Reviews. 2006, Issue 2

Surgery versus Radiation Therapy For Muscle Invasive TCC: Meta-Analysis

- Only 3 quality randomized trials; 493 patients
- 3 yr survival increased from 28% with radiation to 45% with surgery
- 5 yr survival increased from 20% to 36% (OR 2.17, 95% 1.39-3.38)

Shelley MD. Surgery versus radiotherapy for muscle invasive bladder cancer. Cochrane Database of Systematic Reviews. 2001 Issue 4

Lymphadenectomy in Bladder Cancer

- Skinner/Stein: Dissection to include common, presacral, and distal para caval and para aortic nodes
- N1 outcome nearly as good as N0; N3 poor

Survival with Positive Nodes

- 150 N+, M0 patients; 108 without prior CRx
- Median N+ nodes: 2; 12 on average removed
- 70% received adjuvant chemotherapy (P<.01)
- 5 yr OS: **30.9%,** DSS: 45.5% and RFS: 29.7%
- <25% Density: OS: 37.3% v 18.7%;
  RFS: 38.1% v. 10.6% for >25% (P<.02)

Kassouf W: J Urol. 2006, 176:53-7. (MD Anderson)

Skinner Cystectomy: 1971-2001

- 1,359 patients median age 67 (47-78)
- Operative Mortality: 2% (27 patients)
- Overall survival 10 yrs for T2: 47%
- Recurrence free survival, T2: 72%

J Urol. 2006;175:886-9

Limited Node Dissection: Cleveland Clinic Experience

- 385 pts, mean age 62 (31-84) with negative cystectomy margins, 1987-2000
- Obturator and external iliac nodes only
- 12 (2-32) nodes removed
- 45 mo median follow; no neo RT or CRx
- 12% (45) had positive nodes: only 9% overall and recurrence free survival at 5 yr

Dhar NB: BJU Int. 2006 Sep 6; E pub ahead of print

Delay in Cystectomy: Keep it Less Than 12 Weeks

- 13 papers, only 3 (23%) failed to show worse prognosis with delay in surgery
- Increase in stage and/or mortality found in 10 papers
- Consensus: cystectomy should be accomplished in **less than 12 weeks** from the diagnosis of muscle invasive disease

Fahmy NM: Eur Urol. 2006 Jun 13. Epub ahead of print

Conclusions

- Bladder cancer is more common than generally appreciated
- Multiple models are available to test novel treatments
- Translational research is facilitated by the propensity for bladder cancer to recur and the ability to treat and follow bladder cancer transurethrally
- Bladder cancer is responsive to many types of treatment

Conclusions

- Early detection and effective treatment appear to be lowering the mortality of bladder cancer
- Low risk (solitary Ta, G1) patients are best treated with a single instillation of chemo post TUR
- Intermediate risk patients can be treated with chemotherapy (immediate) or BCG
- BCG is never given immediately post op!
- High risk (G3, T1, or CIS) patients are best treated with BCG

Conclusions

- BCG provides superior protection from tumor recurrence
- While BCG is highly effective, it has significant and even life-threatening toxicity, and 50% or more of patients eventually fail treatment.
- Side effects of BCG can be reduced with careful catheterization, dose reduction (x3) and delay
- New, less toxic, more effective bladder cancer treatments are needed

Conclusions

- Patients failing BCG with muscle invasive disease/late cystectomy patients have reduced survival.
- Immediate cystectomy for G3,T1: 45% unsuspected T2 or greater disease.
- Cystectomy for T2 or greater: 45% 5 yr surv.
- BCG for G3, T1: 12% delayed progression.
- Repeat resection of T2 disease: 35% T1 or T0; Cystectomy for these: 65% survival, compared with 82% survival for noncystectomy

Thank You!

for your attention

BCGOncology.com

Combination Vitamins (Oncovite) in Bladder Cancer

- 65 patients post bladder tumor resection randomized to RDA vitamins vs high dose:
  - 40,000 IU Vitamin A
  - 100mg Vitamin B6
  - 2,000mg Vitamin C
  - 400 IU Vitamin E plus 90 mg Zinc
- Tumor recurrence reduced from 91% RDA to 41% at 5 years with Oncovite