

Bladder Cancer Immunotherapy: Progress and Current Limitations

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Phoenix, AZ**

**Hebrew University of Jerusalem
Yissum Technology Transfer
Tel Aviv, September 27, 2005**

www.BCGOncology.com

Bladder Cancer Statistics, 2005

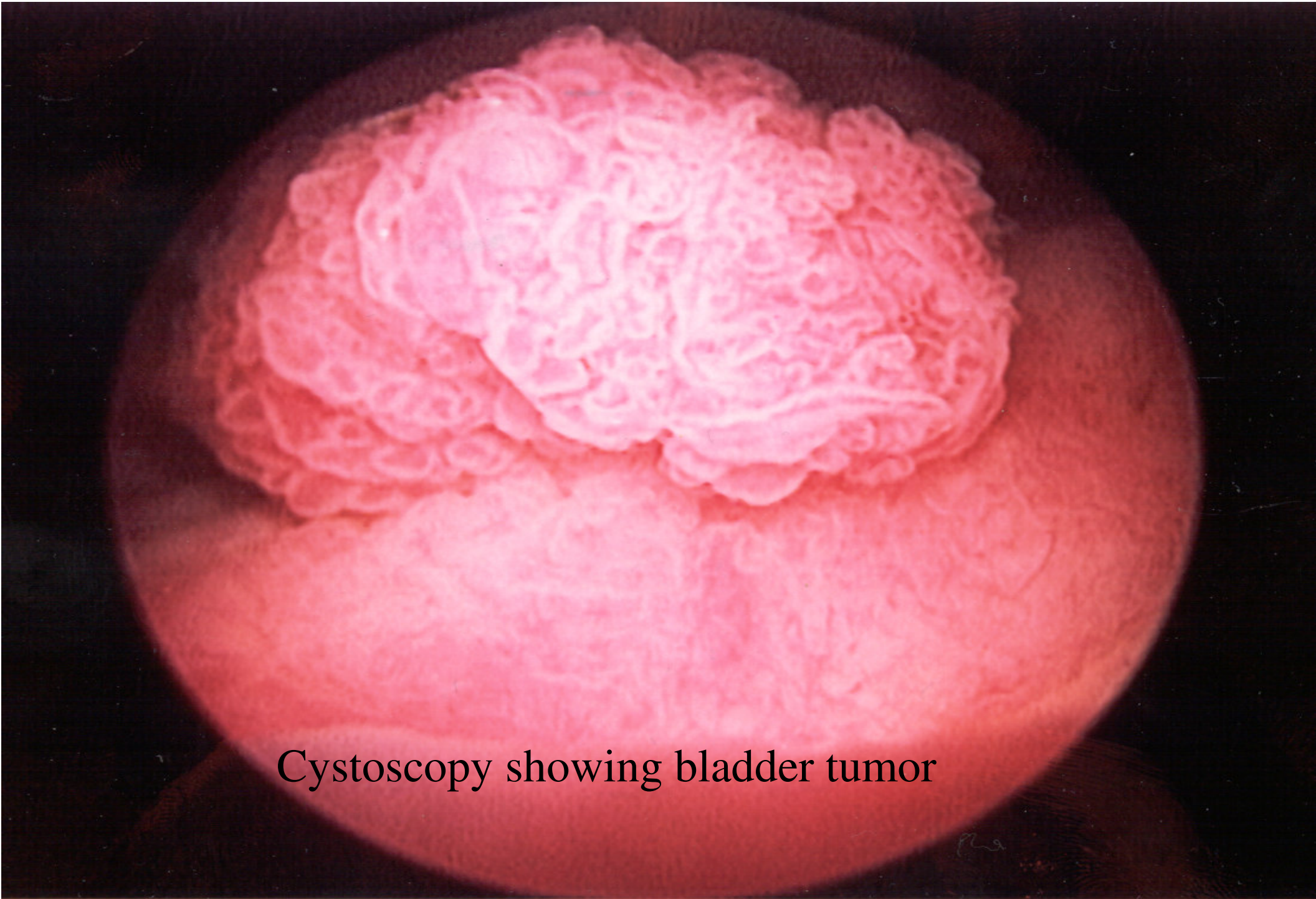
- New Cases: 63,210
 - ▲ Men: 47,010; #4 Women: 16,200 #8
- Estimated Deaths: 13,180
 - ▲ Men: 8,970; #9 Women: 4,210
- Incidence/Mortality: 20.8%
 - ▲ Men: 19% Women: 26%
- Prevalence: More than 600,000 in US

Bladder Cancer, 2005

- Peak Onset: 6th to 8th decades
- Men/women: 3 to 1
- Twice as common in white men compared with African American men
- Genetic mutations: genes on chromosome 9 including p16. Invasion p53, Rb, p21. H19: 84%
- Screening: hematuria detection reduces mortality

Diagnosis

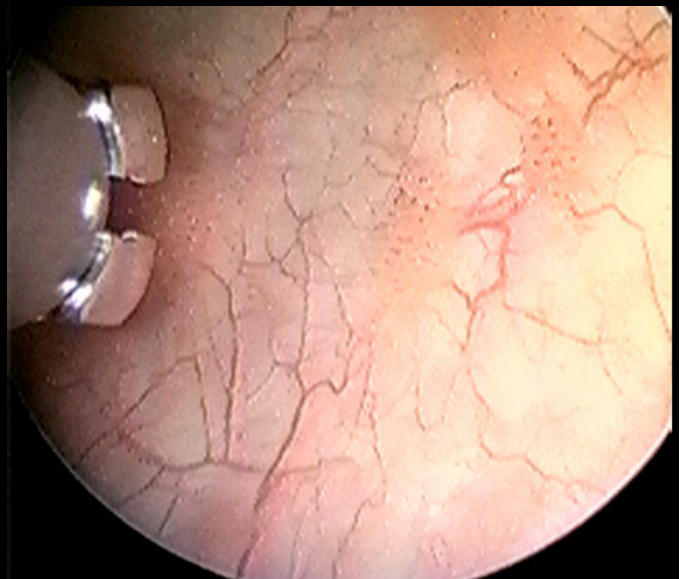
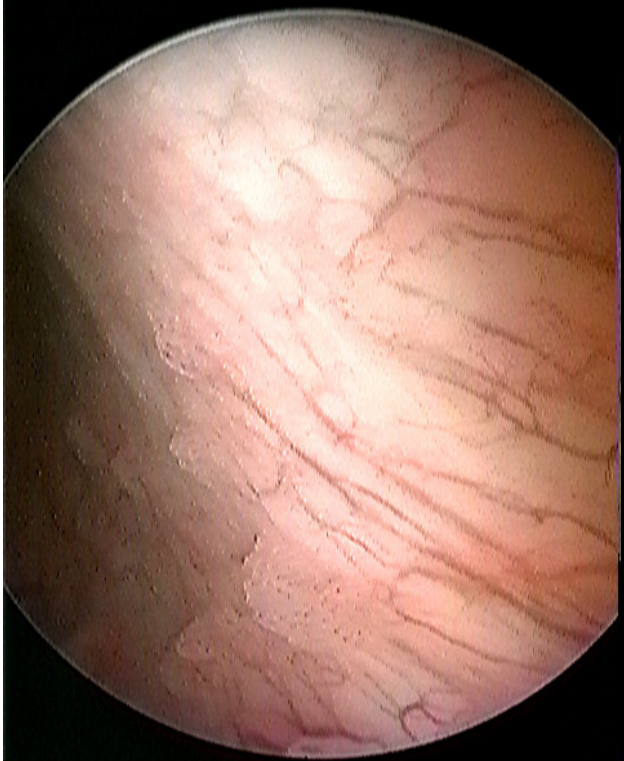
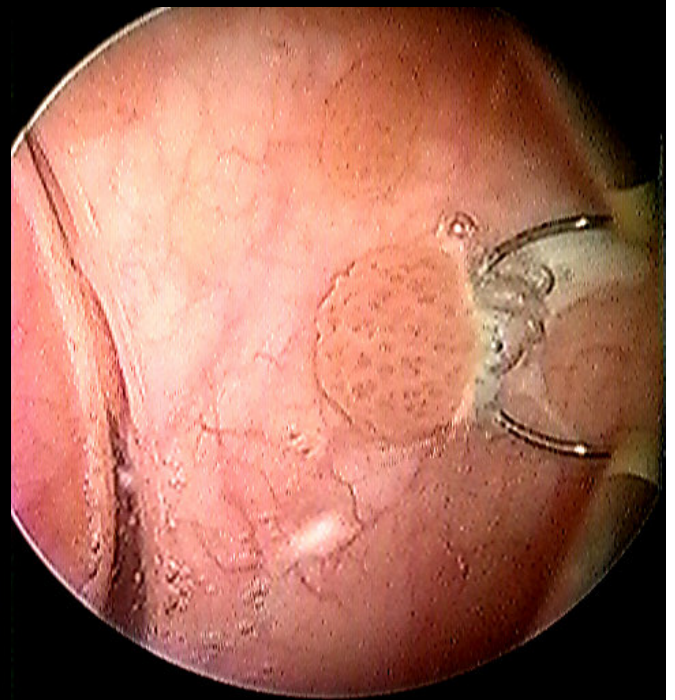
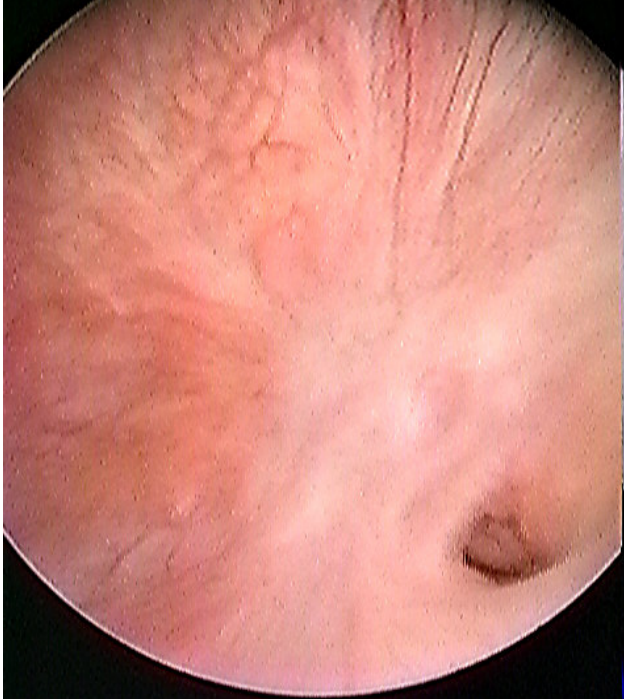
- 85% present with gross or microscopic hematuria
- Cystoscopy is key: papillary tumors are easily seen. High grade, solid, flat or in situ tumors may not be seen
- Urinary Cytology: 80% + sensitivity in high grade tumors with 95% specificity. Insensitive with low grade. Sensitivity improved with FISH
- IVP, CT scan for upper tract evaluation



Cystoscopy showing bladder tumor



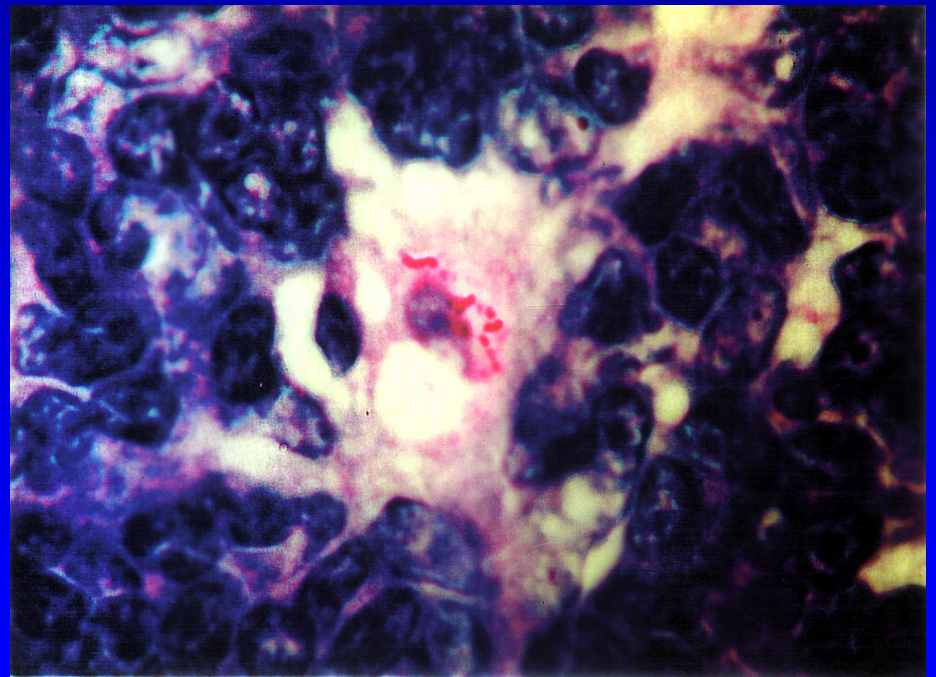
TURBT



Bladder Cancer Immunotherapy is Primarily BCG Immunotherapy

Goals

- Brief History of BCG
- BCG Controlled Trials: vs TUR alone, vs Chemo
- Improving BCG Therapy: Maintenance, BCG + Ifn
- Limitations of BCG
- Prospects for New Agents

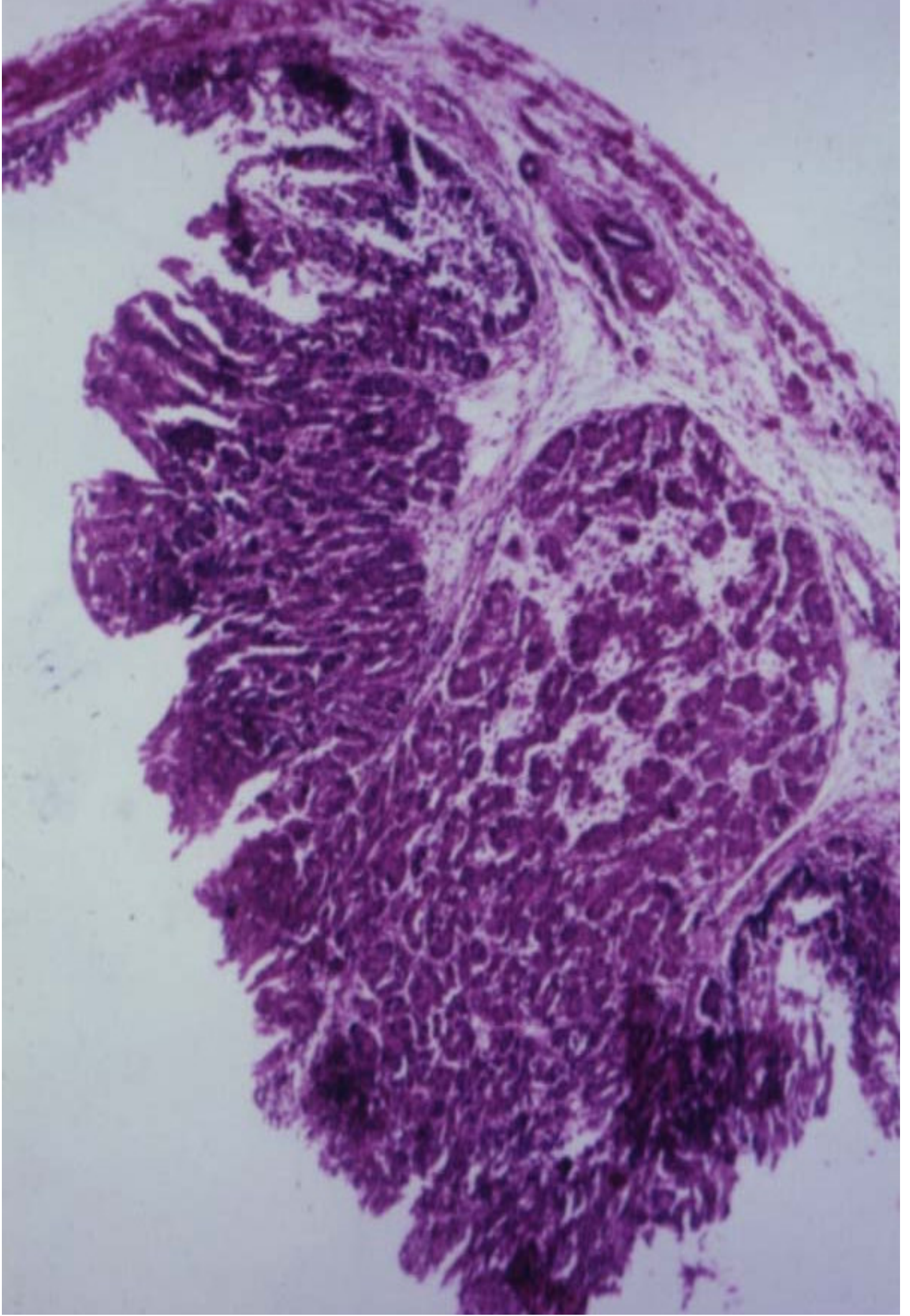


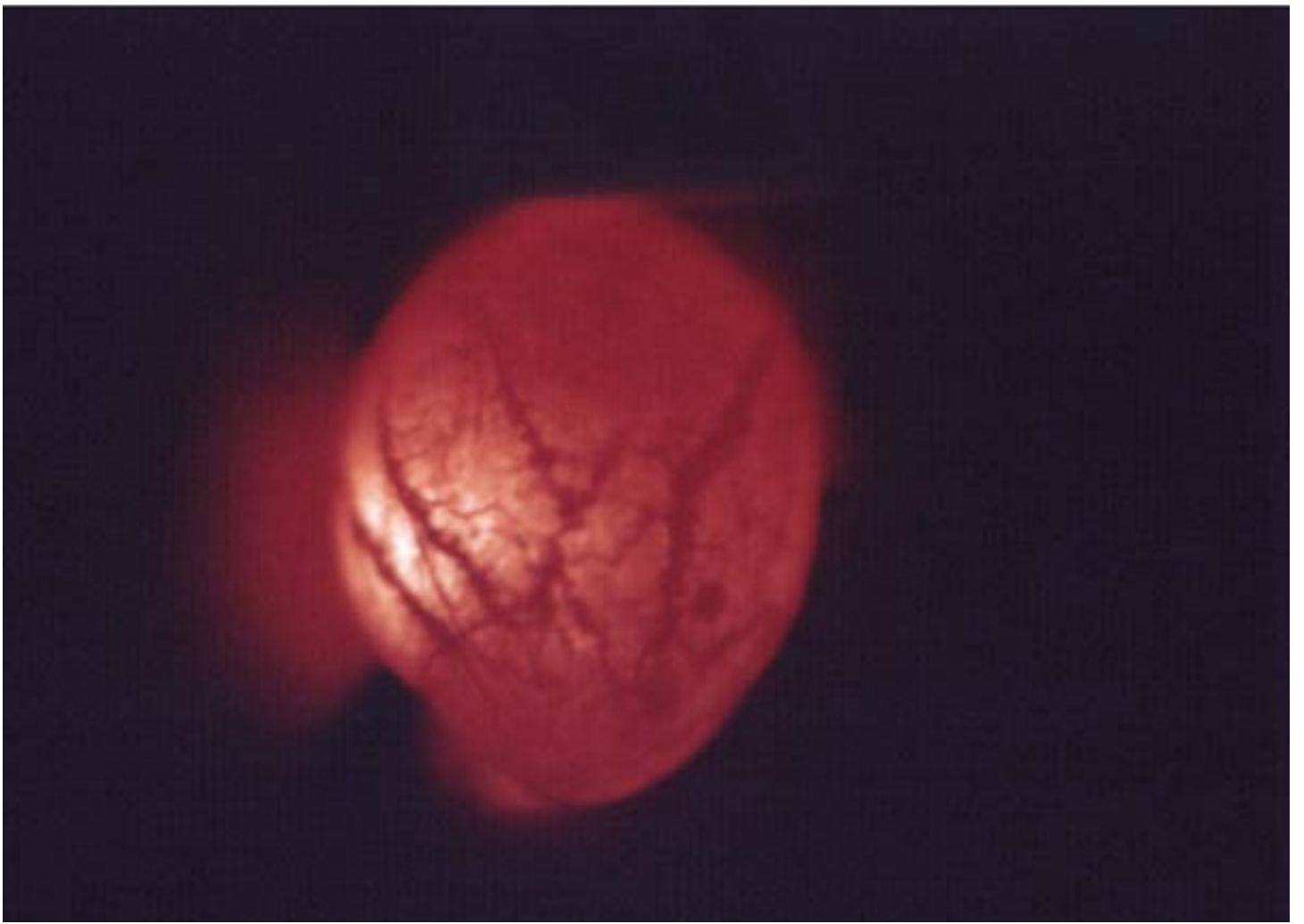
BCG History

- **1921-** Calmette & Guerin successfully tame *M. bovis*
- 1929- Pearl reports TB reduces incidence of CA
- 1930- Lubeck incident brings erroneous scandal
- **1935-** Holmgren reports BCG success in 28 cancer pts
- 1936- Rosenthal reports BCG's profound RE stimulation
- **1950's-** Animal studies confirm efficacy
- 1972- Rosenthal reports = leukemia with vaccination
- **1970's-** Multiple uncontrolled reports of clinical efficacy

BCG History- Bladder Cancer

- **1976-** Morales reports 12 fold reduction in recurrence in 9 patients treated with BCG
- **1973-** Lamm begins controlled animal studies in TCC
- **1978-**NCI controlled trials begin based on Morales' work
- **1980-** Lamm reports first successful controlled trial
- **1982- Current:** Brosman, Netto, Martinez-Pineiro and many others report BCG to be superior to Chemotherapy



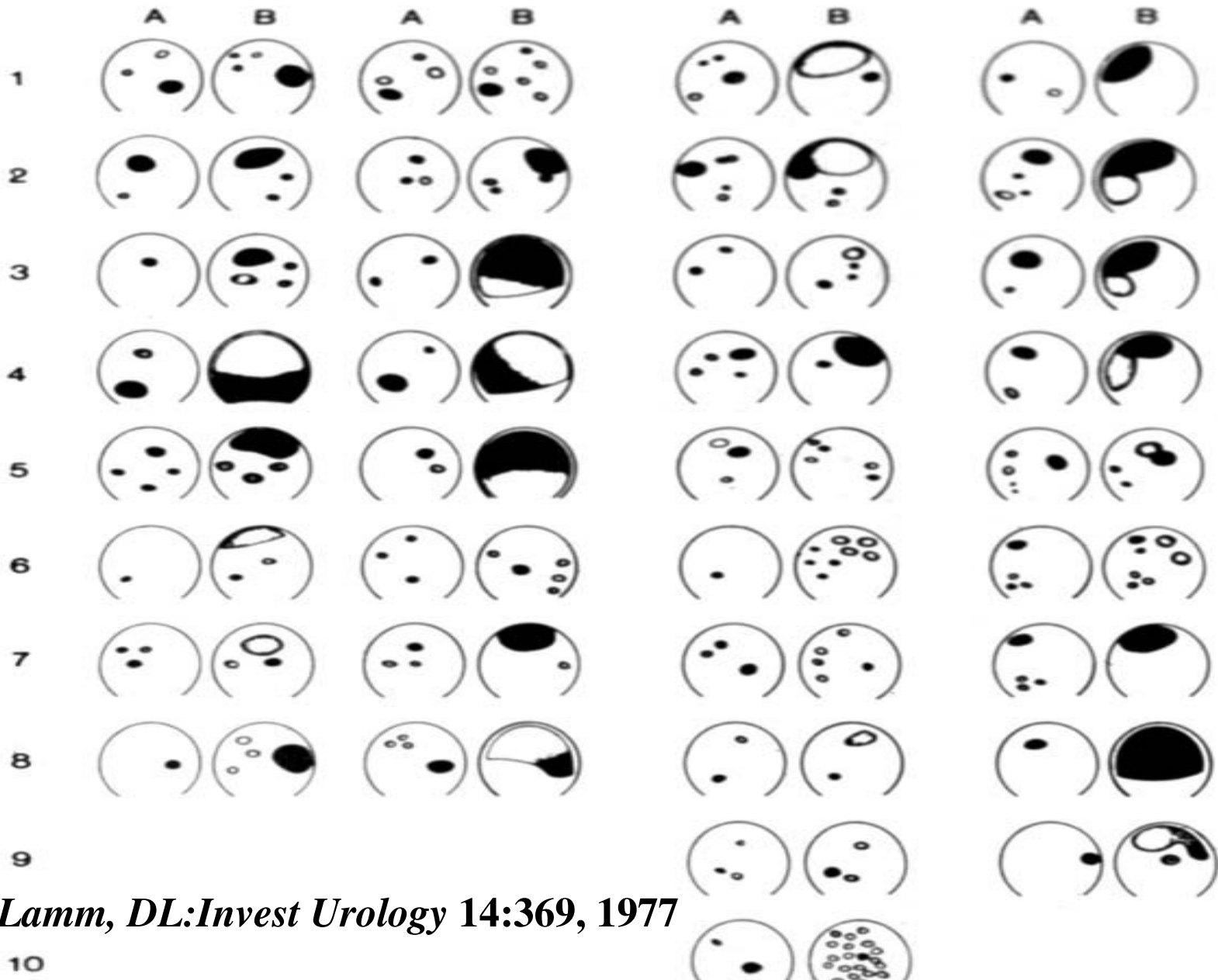


INTRALESIONAL BCG CELL WALL INJECTIONS

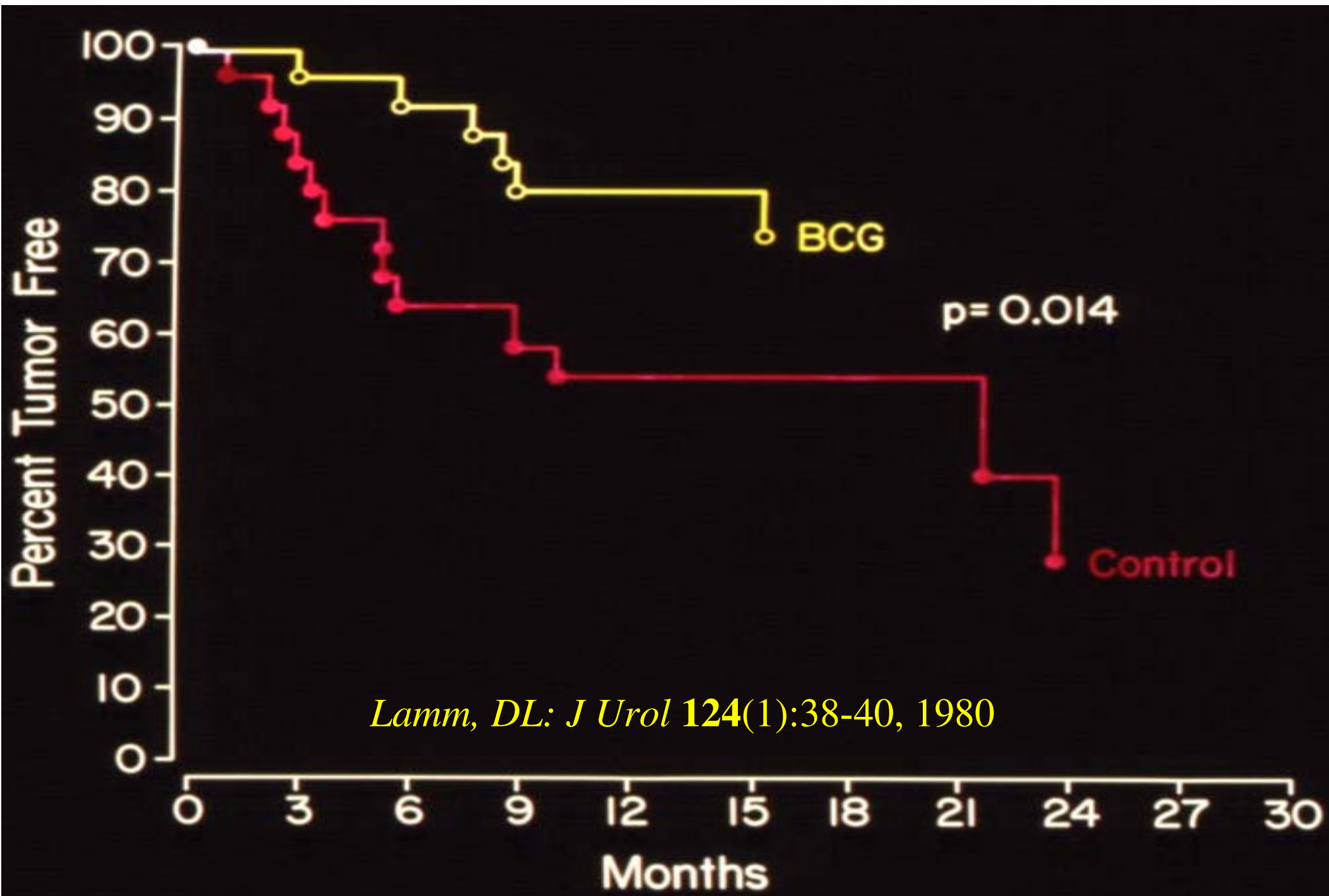
CONTROLS - OIL INJECTION
N=16

SENSITIZED
N=10

UNSENSITIZED
N=9

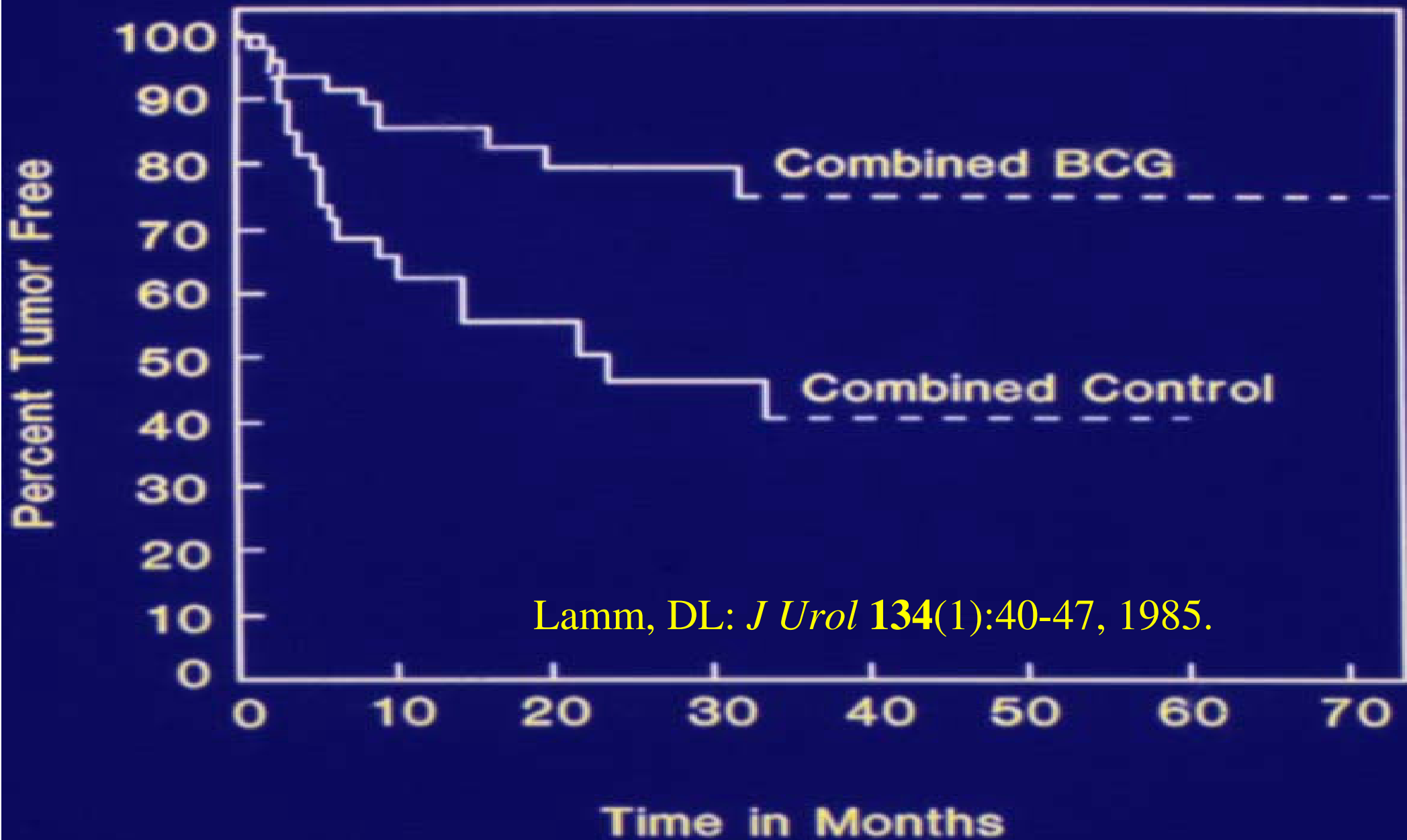


Lamm, DL: Invest Urology 14:369, 1977

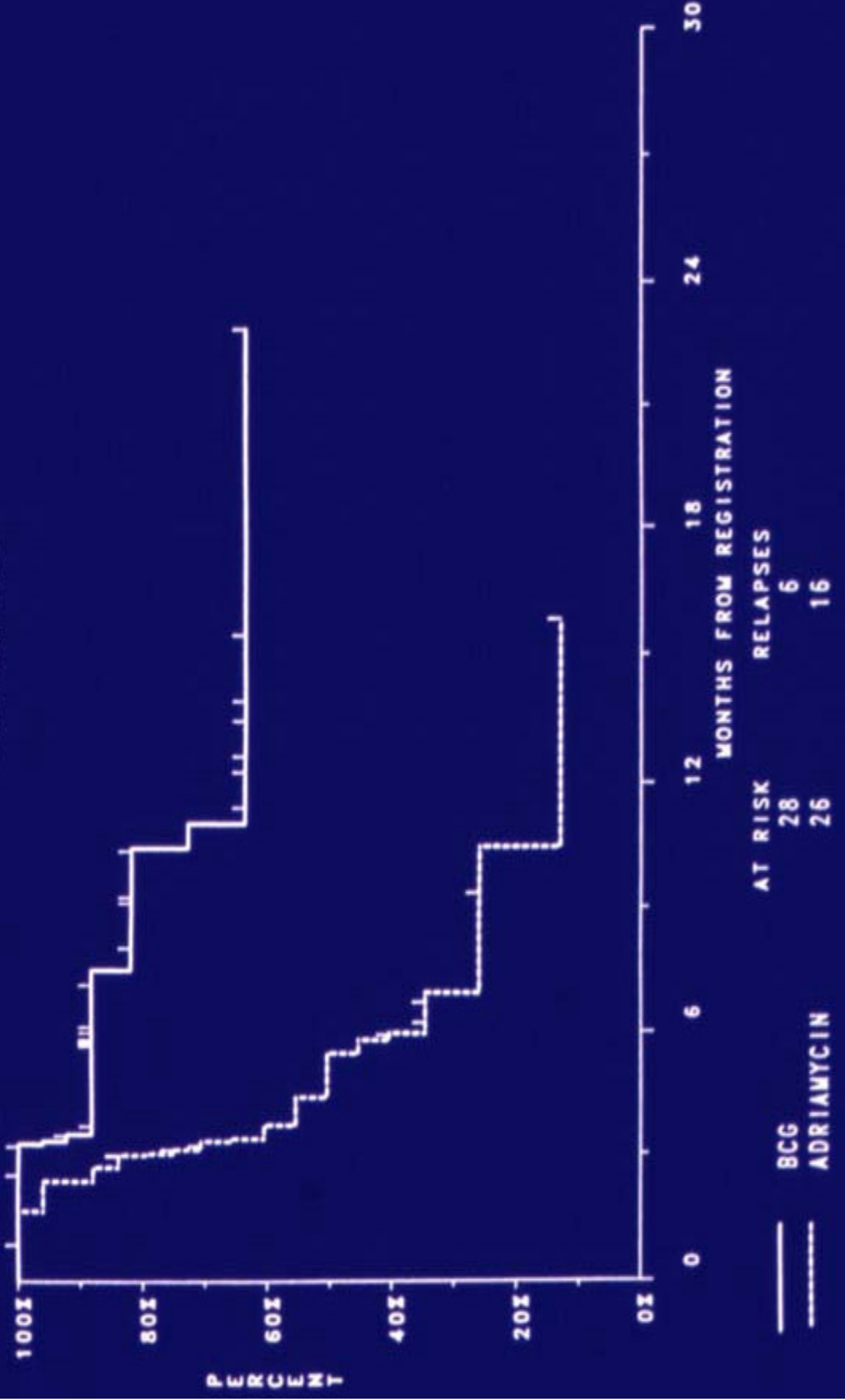


Lamm, DL: J Urol 124(1):38-40, 1980

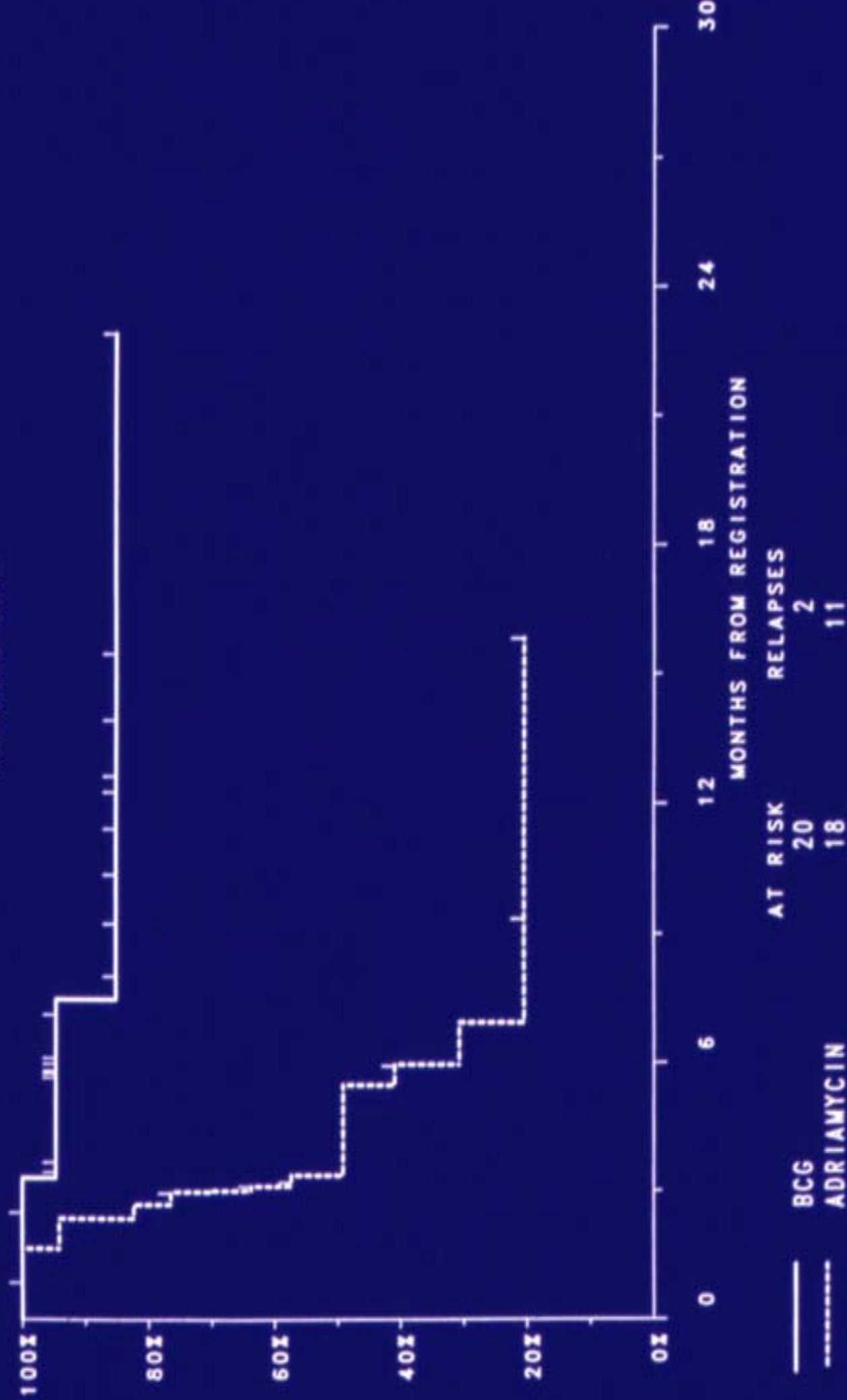
TUMOR RECURRENCE



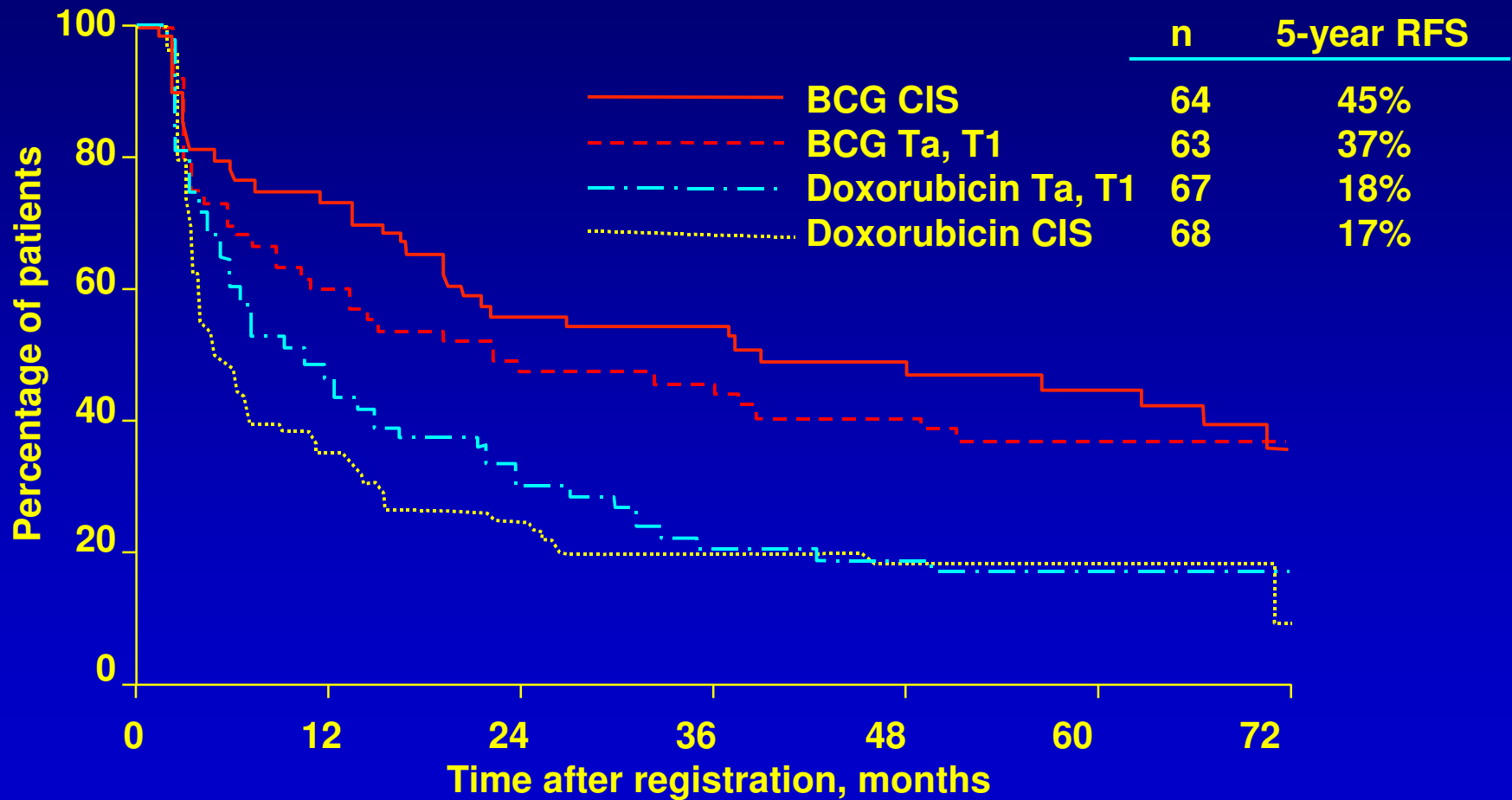
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 DISEASE FREE INTERVAL FOR PATIENTS WITHOUT CIS
 PROTOCOL 8216



SOUTHWEST ONCOLOGY GROUP
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 PROTOCOL 8216



BCG Versus Doxorubicin: Time to Treatment Failure



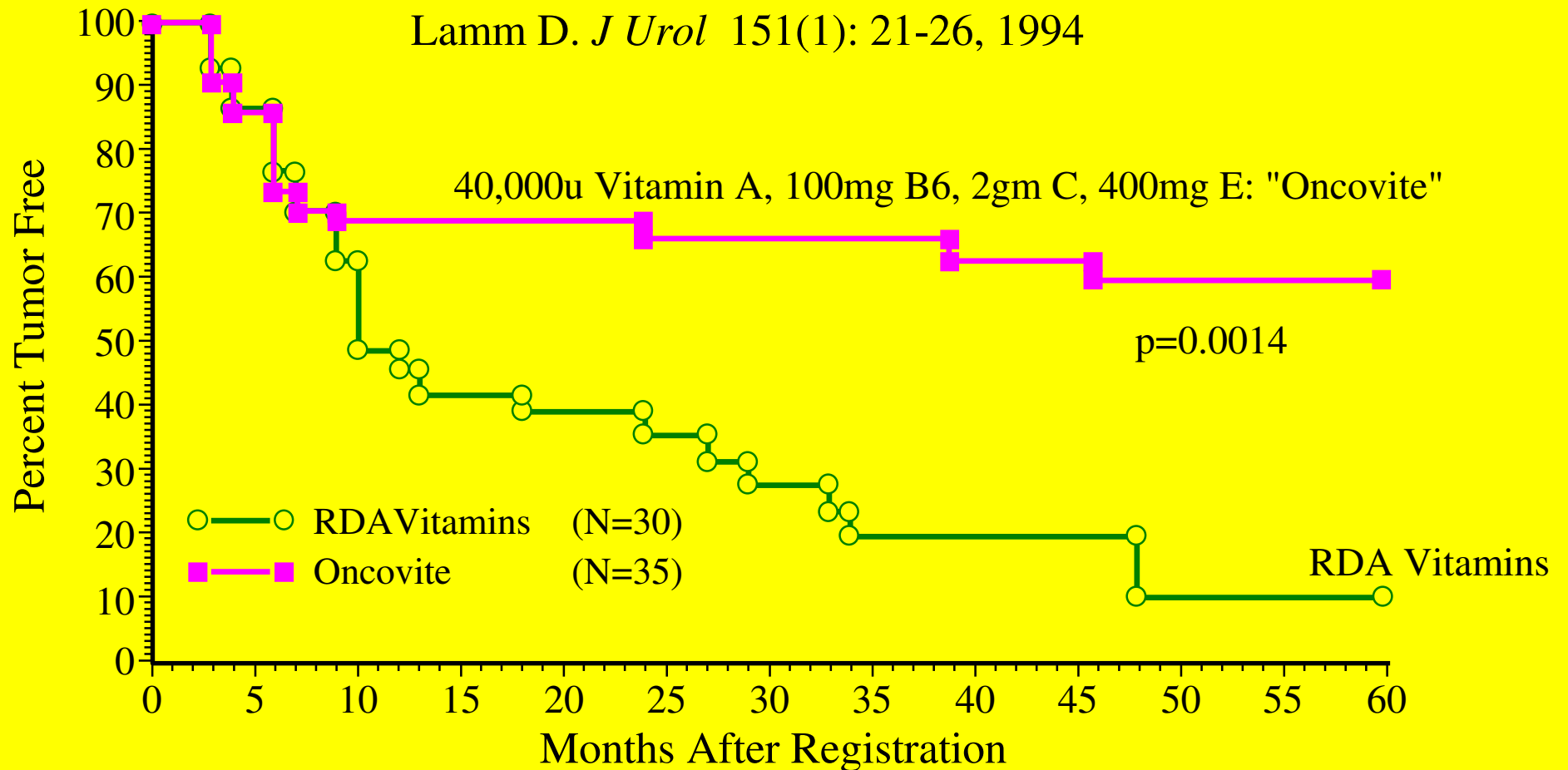
Lamm DL: *N Engl J Med.* 1991;325:1205

Diet, Lifestyle and Environmental Factors

- Diet: low vitamin A, low serum carotene increase risk; increased fat increases risk; soy, garlic, selenium, NSAIDS, and green tea may reduce risk
- Vitamins may be protective: A (differentiating agent); B6; C (antioxidant); E (antioxidant), and possibly folic acid and D

Kaplan Meier Estimate of 5 Year Tumor Free Rate In 65 Patients Receiving Vitamin Supplement and BCG Therapy For Bladder Carcinoma

Lamm D. *J Urol* 151(1): 21-26, 1994



Oncovite (Vitamins A, B6, C & E) in Bladder Cancer

- **Overall recurrence reduced from 80% to 40% (P=0.0011)**
- 42% reduction in recurrence in Ta, T1 TCC
- **53% reduction in low grade (G1, G2) TCC**
- Associated with statistically significant increase in long-term NK cell activity in BCG treated patients

Controlled BCG Trials

<u>Author</u>	<u>no.</u>	<u>NoRx</u>	<u>BCG</u>	<u>Ben.</u>	<u>P</u>
Lamm ' 85	57	52%	20%	32%	<.001
Herr ' 85	86	95%	42%	53%	<.001
Herr (CIS) ' 86	49	100%	35%	65%	<.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:	842	70%	27%	43%	

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
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Randomized BCG vs. MMC Studies

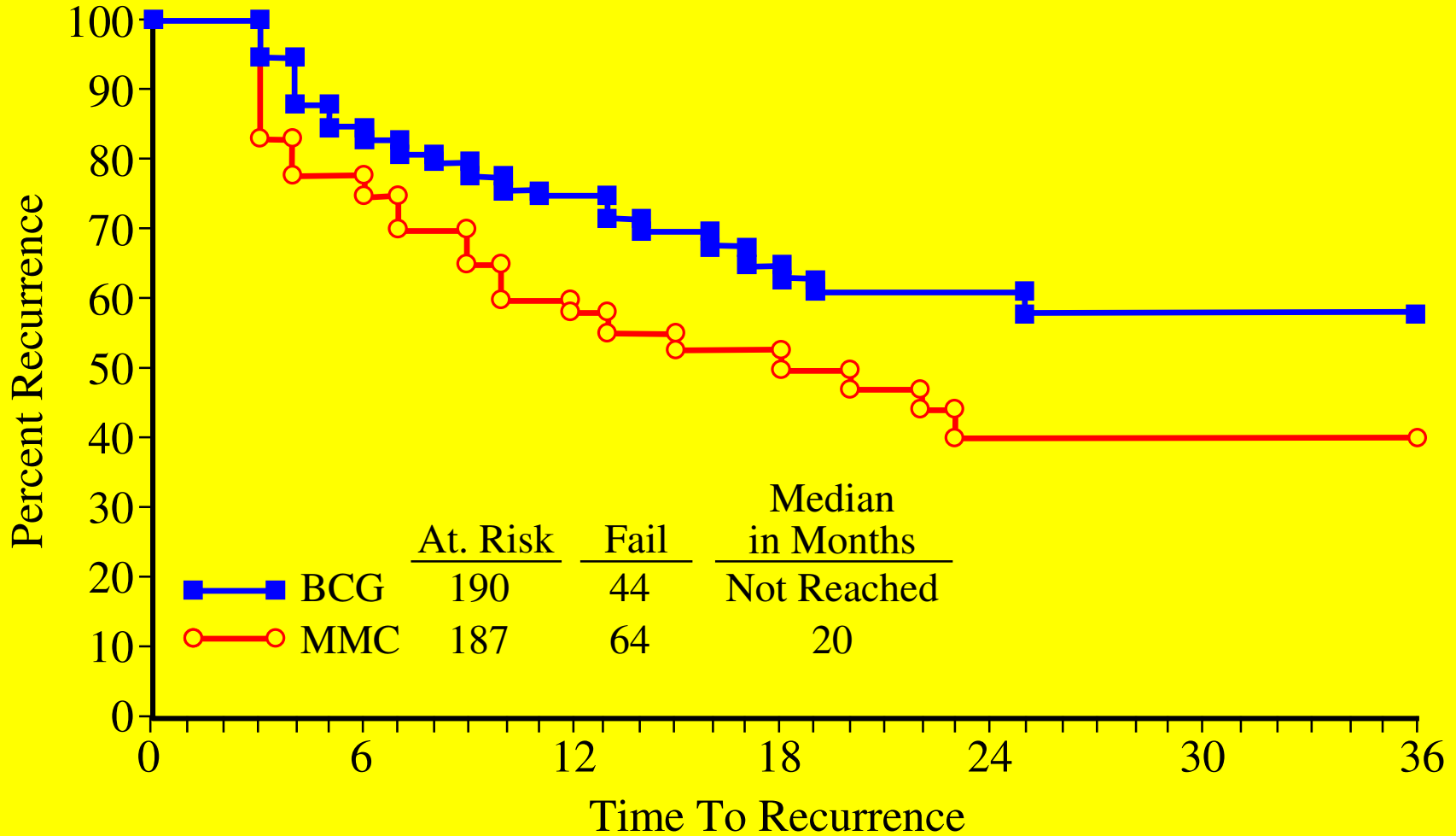
BCG	Rec.	MMC	Δ BCG	P value	Author/year
4 %	vs	34 %	+30	<.01*	Pagano ' 87
28 %	vs	62 %	+34	<.001*	Finnblad ' 89
61 %	vs	80 %	+19	NS	Lee ' 92
47 %	vs	42 %	-5	NS	Witjes ' 94
64 %	vs	42 %	-21		Vegt ' 95
46 %	vs	43 %	-3	NS	" ' 95
43 %	vs	56 %	+9	<.01*	SWOG ' 96
51 %	vs	66 %	+15	<.01*	Malmstr. ' 96
24 %	vs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

Lamm DL: *Urol Oncol* 1:119-126, 1995



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 mitomycin 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 ($P<0.001$).”

Complete Response in CIS Intravesical Chemotherapy

Agent	N	CR%	Range
Thiotepa	89	38%	(20-50%)
Adriamycin	212	48%	(0-88%)
Mitomycin C	196	53%	(0-100%)
Epirubicin	84	56%	
Epi + MMC	21	81%	

Progression in CIS Prior to BCG Immunotherapy

REFERENCE	IN SITU	INVASION (%)	YEARS
Melamed et al (1964)	25	9 (36%)	<5
Koss et al. (1979)	13	7 (54%)	1 to 6
Kulatilake et al (1970)	5	3 (60%)	2
Utz et al (1970)	62	37 (60%)	<5
Farrow, et al (1977)	58	8 (14%)	<5
Sharma et al (1970)	17	14 (82%)	NA
Yates-Bell (1971)	3	3 (100%)	<3
Barlebo et al (1972)	10	0 (0%)	NA
Anderson et al (1973)	15	12 (80%)	NA
Skinner et al (1974)	59	49 (83%)	NA
Riddle et al (1974) (diffuse)	23	18 (78%)	1 to 11
(focal)	13	1 (8%)	1 to 16
Althausen et al (1976)	12	10 (83%)	1.5
Starklint et al (1976)	43	23 (53%)	>1
Herr (1983)	24	23 (50%)	1 to 3
Total	382	206 (54%)	--

Comparison of BCG Preparations in the Treatment of CIS

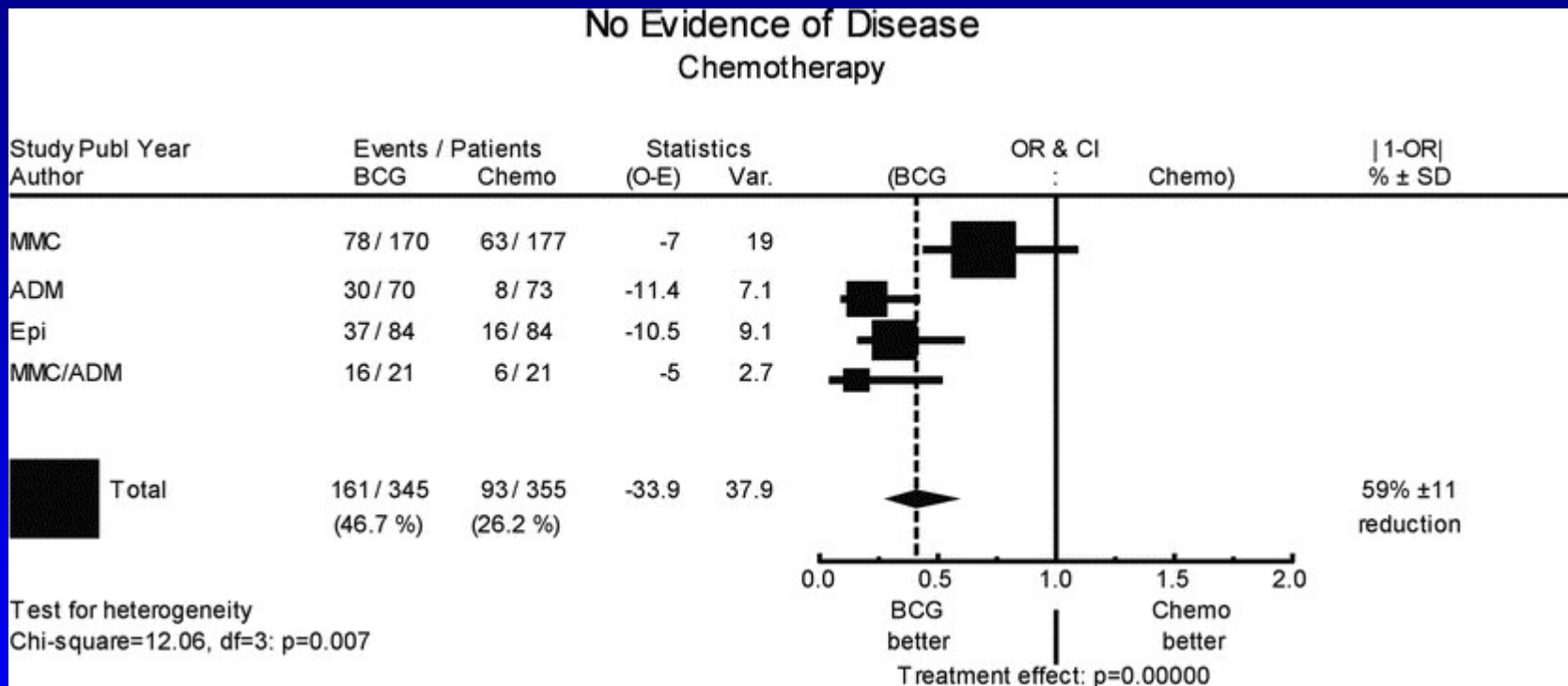
BCG Prep	N	CR %	Range CR
Connaught	450	79%	70% - 92%
Tokyo	111	77%	63% - 84%
Pasteur	230	74%	40% - 80%
Tice	277	71%	56% - 88%
Evans	180	65%	53% - 88%
A Frappier	145	60%	39% - 100%
S African	13	69%	
Danish	42	67%	Total:
Romanian	42	64%	1496 (72%)
RIVM	15	60%	39% - 100%

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.”**

Meta-analysis of BCG versus Chemotherapy in CIS



Sylvester RJ: J Urol. 2005 Jul;174(1):86-91

Carcinoma in situ: SWOG 8507

CIS: 269 Randomized

114 Induction - 230 Evaluable - 116 Maintenance

6 week BCG

6 week BCG

3 mo: 58% CR

P=0.7

55% CR

Observation

3 week BCG

6 mo: 69% CR

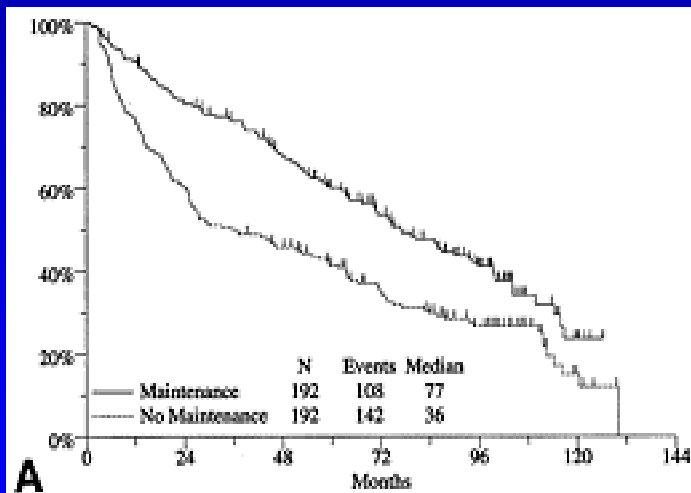
P=0.01

84% CR

26% of CIS failures at 3 mo NED at 6 without further treatment; **64%** with 3wk BCG

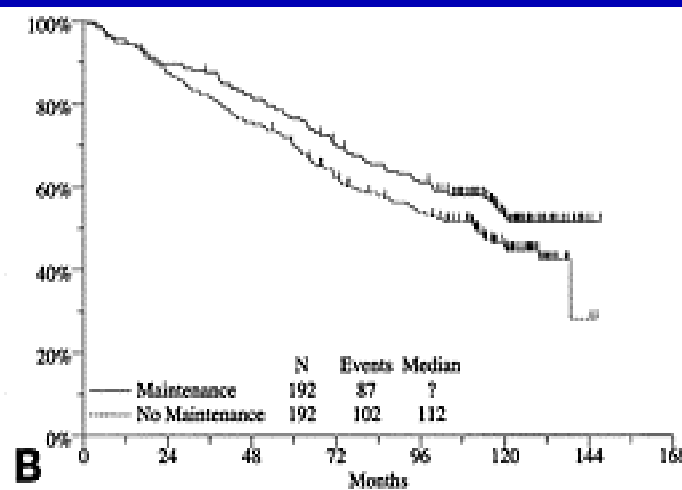
3 Week Maintenance BCG in 550 Randomized, 385 Evaluable Patients

Recurrence -free
Survival



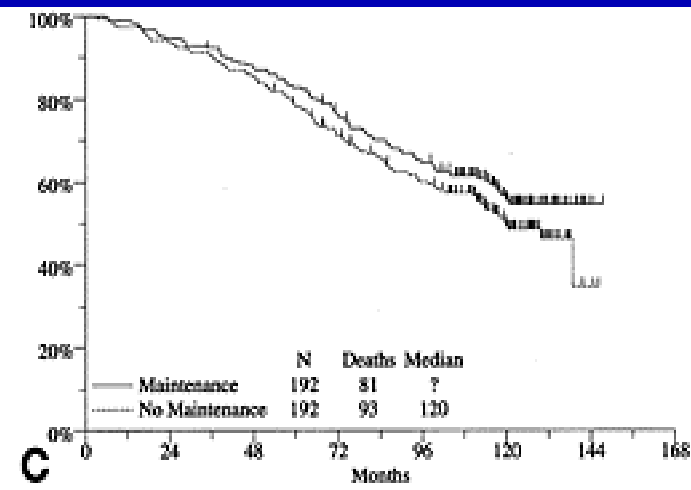
$p < 0.0001$

Worsening -free
Survival



$p = 0.04$

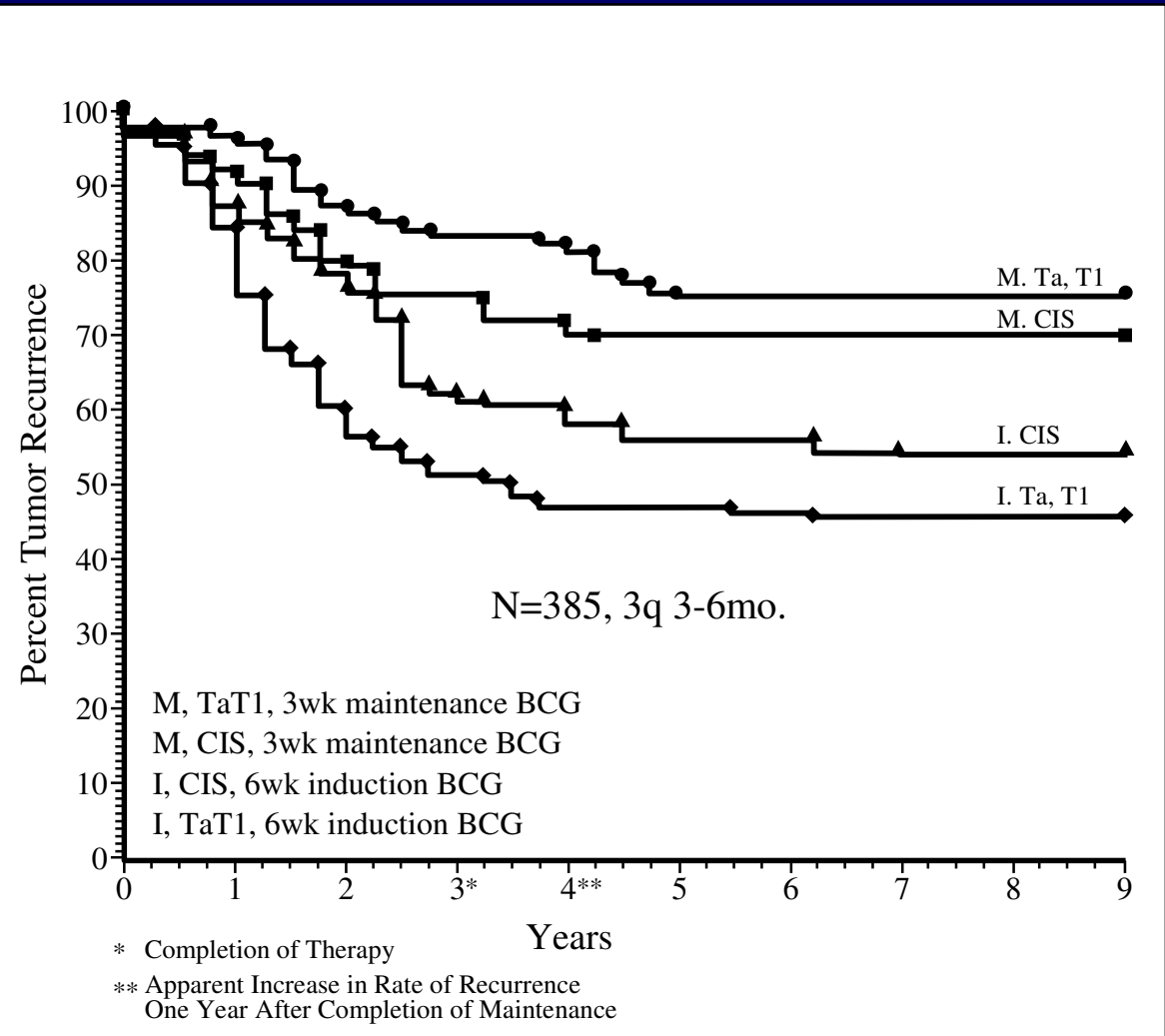
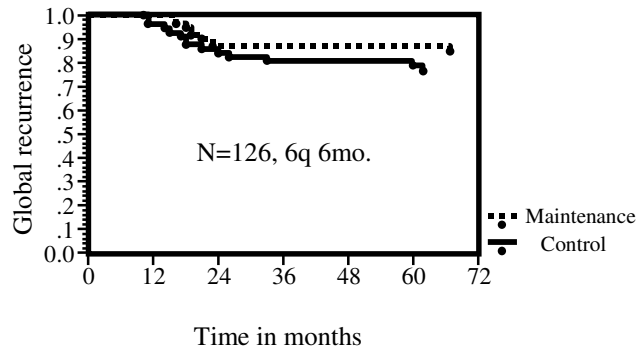
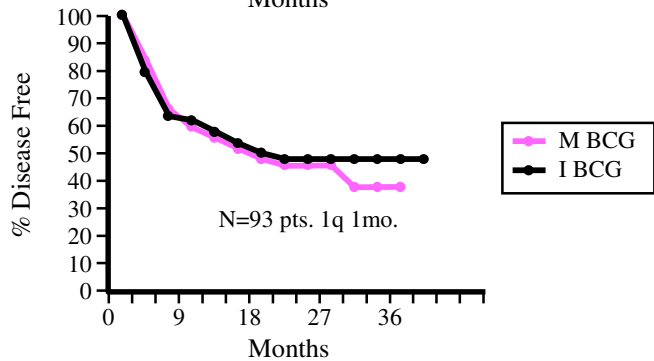
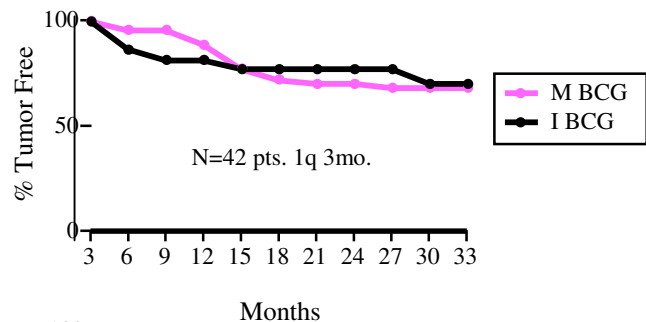
Survival



$p = 0.08$

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

BCG Maintenance: Not Created Equal



3 Weekly Maintenance BCG Schedule: Lamm 2005

Induction Mo: 3 6 12 18 24 36 Yr: 4 5 6 8 10 12

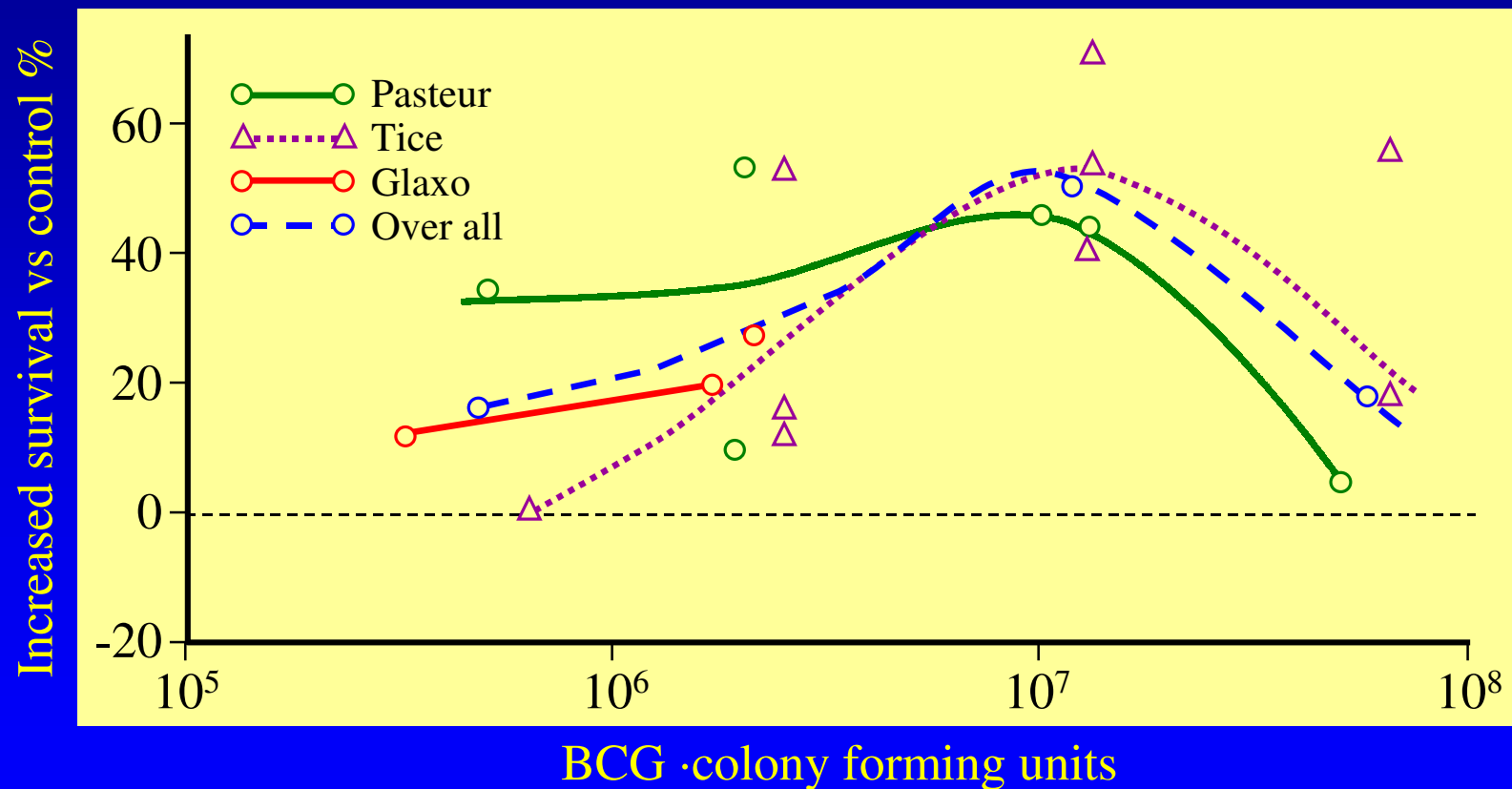
Full x6 1/3x3: * * * * * * * * * * *

Full strength BCG is given weekly for 6 weeks during induction (reduced if needed for increased side effects)

1/3 BCG, reduced to 1/10, 1/30, 1/100th if needed due to increased side effects, given at 3,6,12,18,24, and 36 months, then years 4, 5, 6, 8, 10 and 12 years in G3/CIS

Dose-Response Curve to BCG (in mice)

Individual responses and preparations vary, but
too little or too much BCG reduces effect



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

Progression: Maintenance BCG

	Patients	No BCG	BCG	OR
No Maint	1049	10.3%	10.8%	1.28
Maintenance	3814	14.7%	9.5%	0.63

Test for heterogeneity: $P = 0.008$

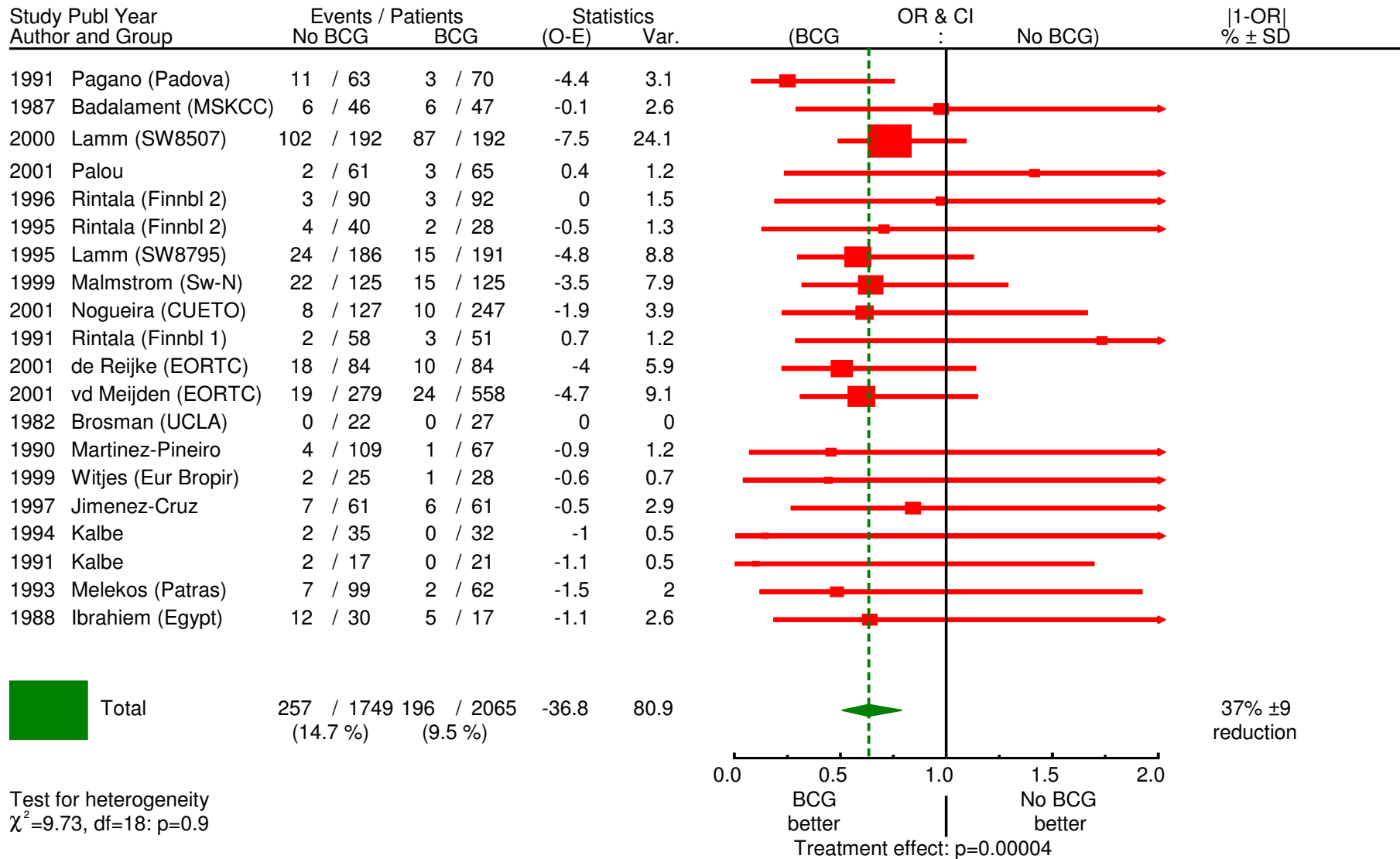
BCG was only effective in trials with maintenance, where it reduced the risk of progression by 37%

$p = 0.00004.$

Sylvester RJ: J Urol. 2002 Nov;168(5):1964-70.

Meta Analysis of 24 Randomized Trials

Progression All Studies With Maintenance



Survival

Death	Patients	No BCG	BCG	Total	OR
All	2930	26.7%	23.2%	24.8%	0.89
Bladder	2370	7.7%	5.6%	6.5%	0.81

The reductions in the odds of death, 11% overall and 19% bladder cancer, are not statistically significant, as might be expected with 2.5 year mean follow up

Sylvester RJ: J Urol. 2002 Nov;168(5):1964-70.
Meta Analysis of 24 Randomized Trials

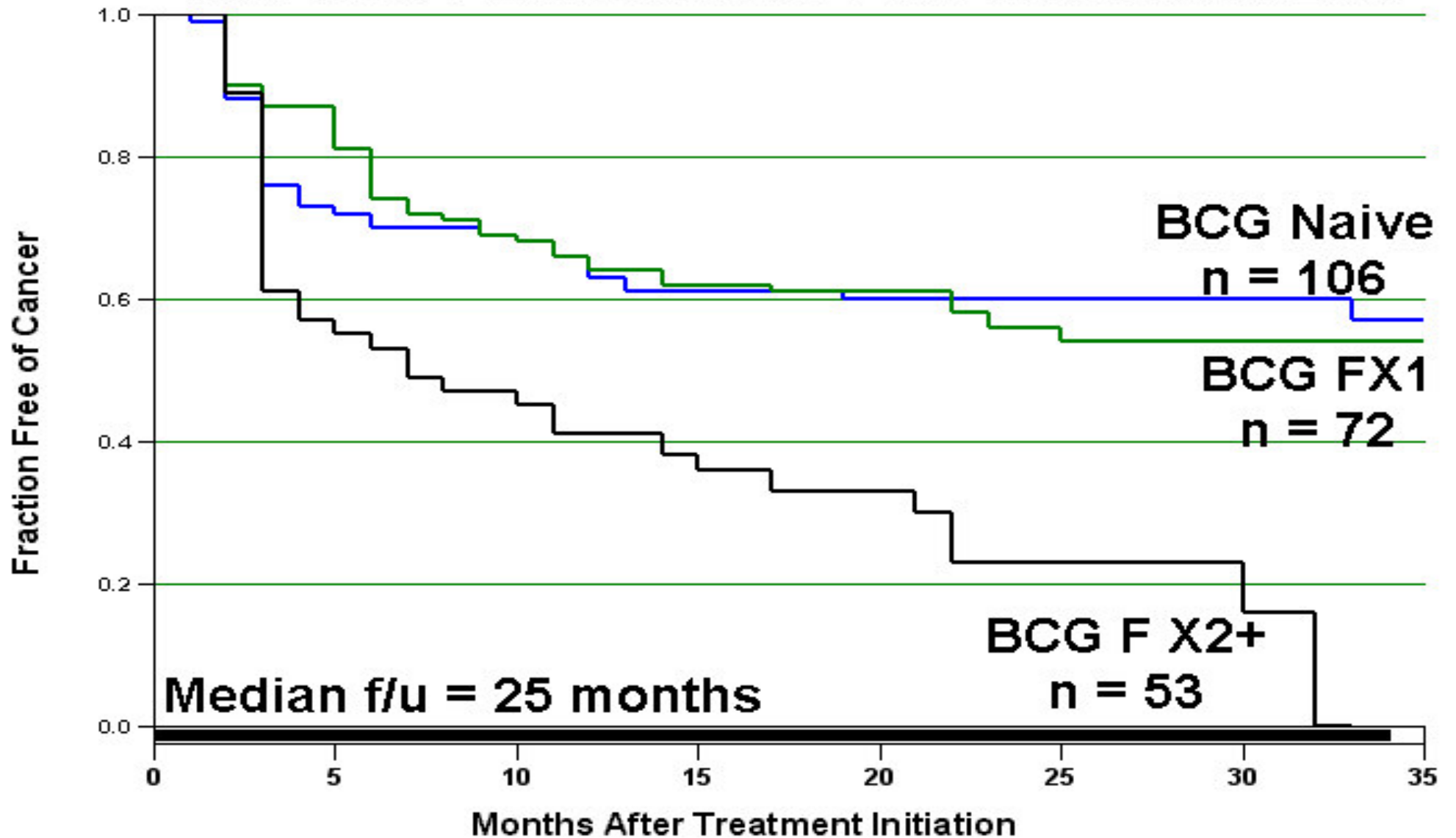
Limitations of BCG Immunotherapy: 50 to 80% Eventually Fail

- Early failure to respond
 - ▲ Excess or remote tumors
 - ▲ Rapidly dividing/growing tumor
 - ▲ Low grade, “non -antigenic” tumors
 - ▲ Unresponsive host
- Late recurrence: immunosuppression, resistance
- Toxicity

Treatment of BCG Failure

- **Chemotherapy for BCG failures provides poor response rates**
 - \cong 19% for MMC post BCG
 - Malmstrom, *J Urol*, 2001
- **Low Dose BCG after one cycle BCG failure provides 60% durable CR (same as BCG naive)**

Freedom from Disease in Patients with CIS Treated with BCG + IFN based on Prior Courses of BCG



Esuvaranathan: Singapore Randomized Trial- Full Dose BCG v 1/3 BCG v 1/3 BCG+Ifn alpha

65 patients randomized to full dose **Evan's** BCG vs. 1/3 dose vs. 1/3 dose BCG plus **10 MU Intron A**

	9 mo. Rec	20 mo. Rec	
Full Dose BCG:	32%	48%	
1/3 Dose BCG:	12%	24%	*P=0.035 vs
1/3 BCG+ Ifn:	12%	12%*	Full dose BCG

Subsequent randomization to full dose BCG vs. BCG+Ifn, 130 pts:

	Mean TTR	5yr KM% Rec. Free
Full Dose BCG (N=60):	58.5 mo.	51% (49% rec)
1/3 Dose BCG (N=29):	61.8 mo.	66% (34%)
1/3 BCG+ Ifn (N=41):	71.8 mo.	79% (21%)

Complications of BCG Therapy in 2,569 Patients

	Total	Tice	Connaught
Fever	75(2.9%)	4.7%	4.7%
G. Prost	23(0.9%)	1.8%	1.0%
Pneum/hep.	18(0.7%)	.4%	.8%
Arthralgia	12(0.6%)	.7%	.1%
Hematuria	24(1.0%)	.3%	.6%
Rash	8(0.3%)	.4%	0
Uret. Obstr.	8(0.3%)	.6%	.4%
Epididymitis	10(0.4%)	.4%	0
Contr. blad.	6(0.2%)	0	.3%
Renal abscess	2(0.1%)	0	0
Sepsis	10(0.4%)	.1%	.4%

Lamm DL. Urol Clin North Am. 1992; 19:565-7



Megathura crenulata

Early Comparison KLH Trials

Treatment	R/100 pt mo	N	Rec %
MMC	9.3	23	39%
KLH 10mg	3.3	21	14%
Epodyl	4.8	46	35%
KLH 20 mg	6.5	38	21%

Jurincic, 1988; Flamm, 1990

Purified vs Crude KLH vs BCG

Treatment	Incidence	Volume	Survival
Pure KLH	4/10	1900mm	5
Crude KLH	0/10**	230 **	10 **
BCG	2/10*	71 **	9 *
Saline	8/10	3400	3

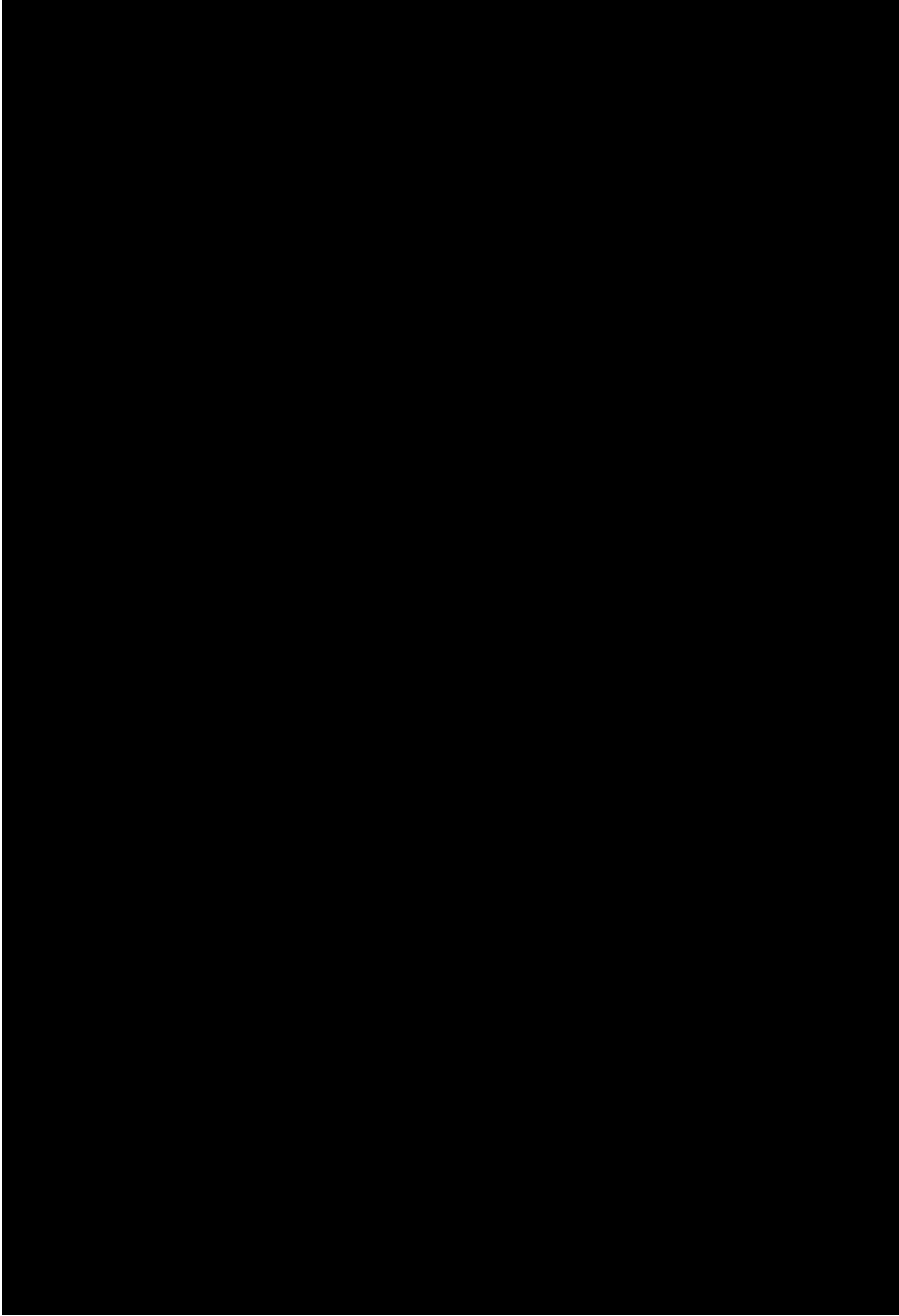
* P<0.012; ** P<0.002

Complete Response to KLH by Disease Category

Stage	CR (N)	CR (%)
CIS	9	50%
Ta, T1, CIS	4	33%
Ta, T1	3	20%
Total	16	36%

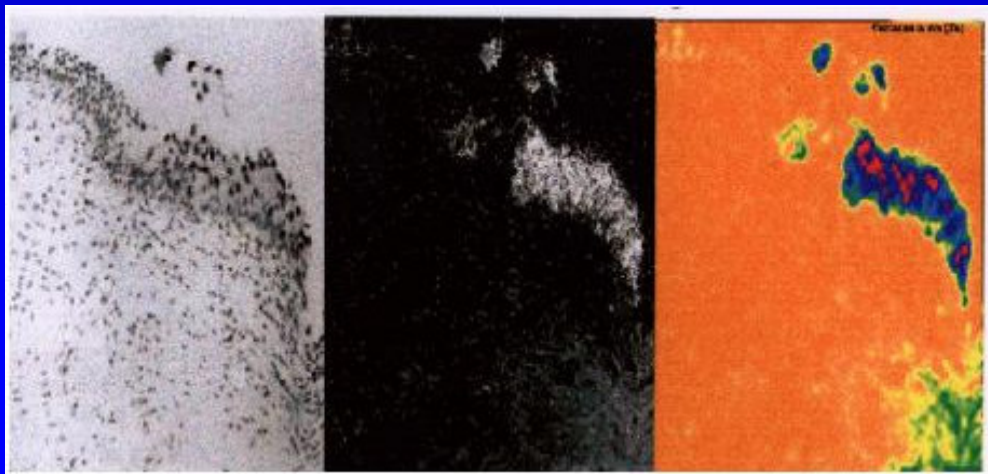
Conclusions

- Bladder Cancer is immunoresponsive and an excellent model for drug development.
- BCG immunotherapy is superior to chemotherapy and reduces progression, but 50-80% fail.
- Maintenance schedules, vitamins, and interferon may improve response.
- New agents such as KLH and others hold promise for reduced toxicity, and **new approaches such as DNA-based therapy are greatly needed!**

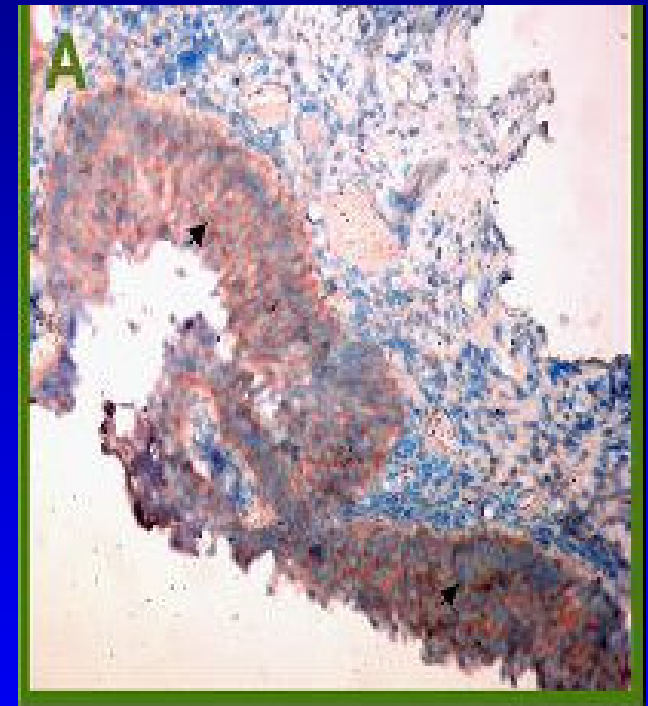


H19 Expression in Bladder Cancer

- 84% of TCC express H19
- Levels are nearly undetectable in surrounding normal urothelium



CIS H19 ISH Color Intensity



G2 TCC with H19 Stain

What is the Best Induction Schedule ?

- Six weekly instillations: excellent but clearly suboptimal
- Immune stimulation peaks at 6 weeks
- Continued treatment beyond 6 weeks can suppress the immune response
- With retreatment, stimulation peaks at 3wks
- Controlled trial of "6" vs "6+3" in CIS shows <CR from 69% to 84% (P<0.01)

Why Not Give Monthly BCG Maintenance ?

- Historical and controlled studies show no advantage over 6 week induction
- Toxicity is increased over induction
- There is no biological or immunological rationale for the monthly schedule
- Immune suppression may occur

Percutaneous BCG ?

- Two studies failed to demonstrate benefit
- 40-60% of patients convert PPD skin test after intravesical BCG
- More than 90% convert with I.D. BCG
- Lamm ' 85 and Torrence ' 88:
- 17/55 (31%) recurrence with PPD conversion, 51/82 (62%) recurrence with no conversion $P=0.0225$
- CR in CIS increased from 49% to 77% with PPD conversion (SWOG, $P<0.001$)

Optimal BCG Retreatment

- "6+6" should be avoided, unless the interval since last treatment has been long (many years) and little or no side effects occurred
- If a second six week course is given one cannot distinguish decreased sensitivity to BCG from iatrogenic immunosuppression
- For repeat BCG, think "3 plus 3"

Toxicity of Maintenance BCG

- Log dose reductions (1/3, 1/10, 1/30, 1/100th) or stopping maintenance BCG appears to prevent toxicity
- Side effects are not required to receive the benefit of maintenance BCG

Treatment of BCG Sepsis

- Isoniazid 300mg, rifampin 600mg, and ethambutol 1200mg daily plus a fluoroquinolone or an aminoglycoside
- Prednisone 40mg daily (higher doses sometimes are required)
- Taper steroid slowly when patient improves
- Resume steroids if symptoms recur after taper
- Continue triple antibiotics for 3-6 months
- No more BCG