Current Superficial (TA,T1, CIS) Bladder Cancer Management

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Satellite Meeting, 5/22/07, AUA Anaheim, CA

Current Practice

- MMC and BCG: risk factors
- Management of Recurrence: treatment failures
- Biomarkers: research or practice?
- Future Therapies: currently probable?

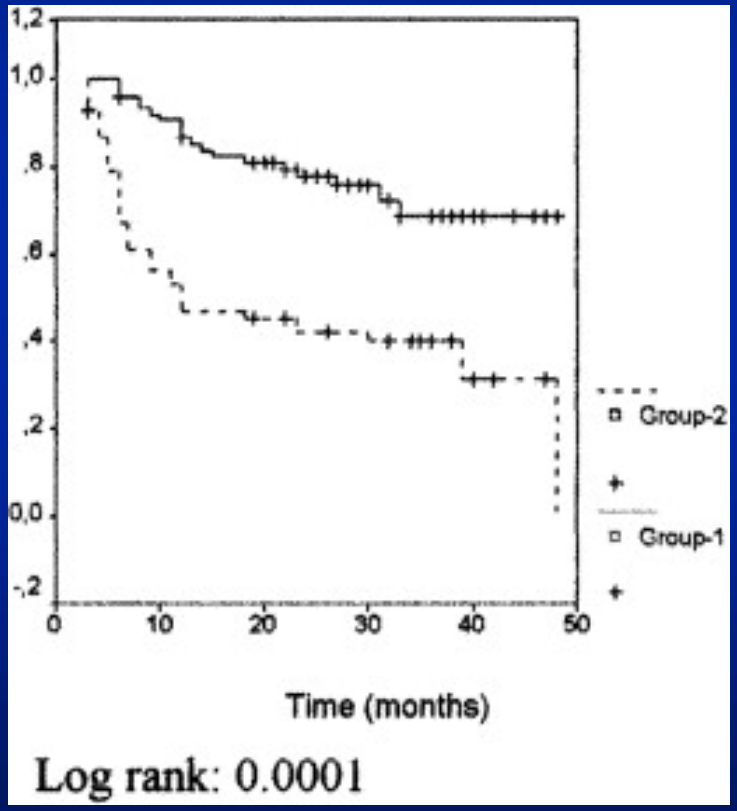
Key Management Points/Controversies

- TUR: technique and repeat
- Immediate postoperative chemotherapy
- Risk assessment/treatment by risk group
- Low risk: optimal intravesical chemotherapy
- High risk: optimal BCG immunotherapy
- Early Cystectomy rather than BCG for G3,T1
- Recurrence:Definition/management of failures
- What's new: combo chemo, electomotive /hyperthermic chemo, new/combined IRx

TURBT:
Get it all the ***Second*** Time?

- ~40% (26-83%) have disease at re-TUR and 2-28% are upstaged to T2 (Miladi M: 2003, Eur Urol. 43:241.)
- More extensive resection can reduce disease at re-TUR (Langbein L: 2006, MPP. 15:215.)
- Flamm J: "Residual" disease common even with negative margins at initial TUR (personal communication)
- 10-year disease-specific survival was 76% in 99 T2 pts who received TUR as definitive Rx (Herr HW: 2001, JCO. 19:89.)
- Bottom line: If you can't get it all the first time, get it the second time!

Randomized Trial of Repeat TUR with Immediate Post op MMC

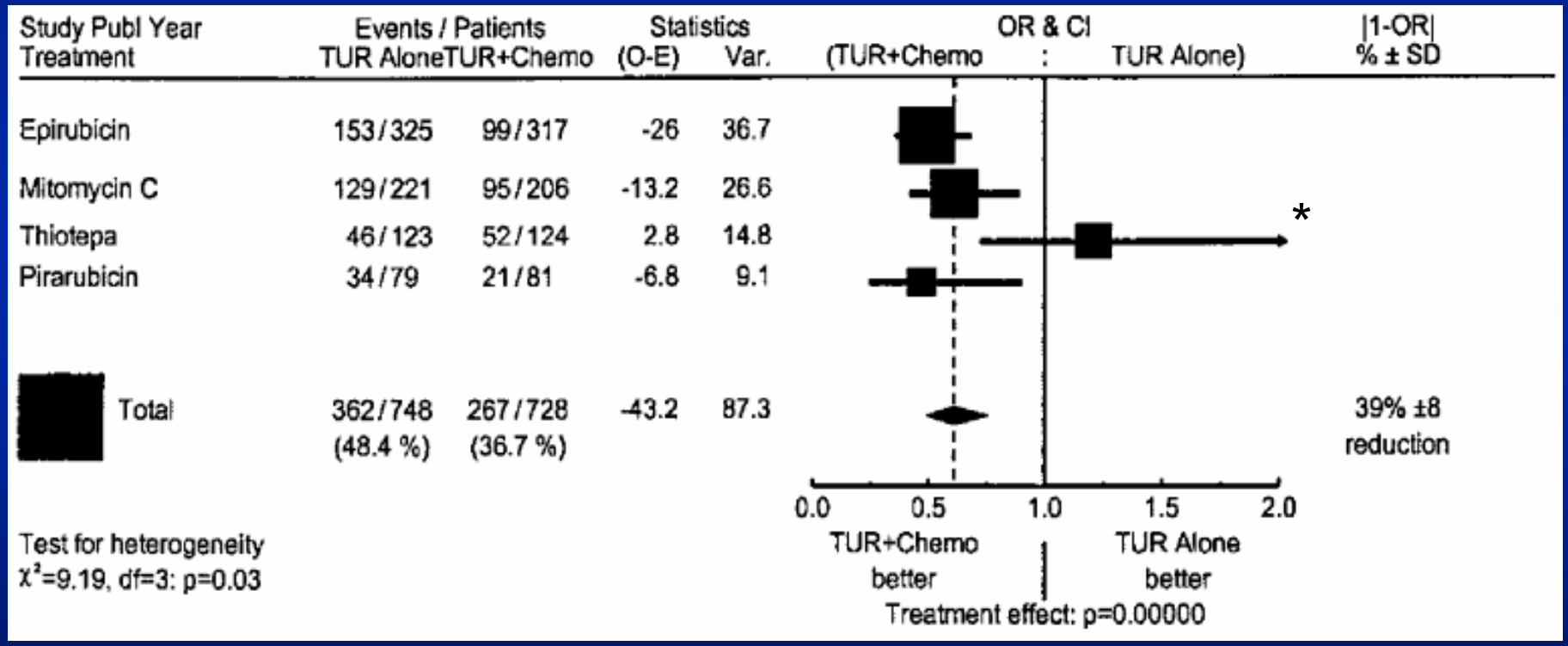


- 142 T1 TCC randomized re-TUR or not
- All received 40mg MMC after 1st or 2nd TUR 2-6 wks later, then x7
- Recurrence: 19/74 (26%) group 1 and 43/68 (63%) group 2
- Median RFS 27 mo (6 -48) group 1 vs 12 mo (3-48) in group 2 ($p<0.001$ for high grade tumors)

Divrik RT: J Urol. 2006 May;175(5):1641

Perioperative Chemotherapy

Forest Plot of Recurrence



* Thiotepa study included dilute, ineffective preparation

Sylvester RJ, et al. *J Urol.* 2004;171:2186-2190.

Meta-Analysis: Immediate Postoperative Intravesical Chemotherapy

- 1476 patients in 7 randomized clinical trials
- Tumor recurrence reduced from 48.4% to 36.7% (OR 0.61, P<0.0001)
- **Effect may be less in multiple than solitary tumors: 65.2% versus 35.8% recurrence.**
- Benefit is significant (& cost effective) even in solitary, low-grade tumors.

Sylvester RJ. J Urol. 2004;171:2186-90

Risk Factors in Superficial Bladder Cancer

Recurrence: ***Multiplicity*** is the best predictor

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

Progression: ***Lamina propria invasion***

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

Mortality: ***Grade*** is the best predictor

- 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: Low Grade (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

EORTC Risk Tables For Stage Ta T1 Bladder Cancer

EORTC Risk Tables for Stage Ta T1 Bladder Cancer

Prior Reccurence Rate
- ○ Primary
- ◉ Recurrent <= 1 per year
- ○ Recurrent > 1 per year

Number of Tumors
- ○ 1
- ◉ 2 to 7
- ○ 8 or more

Tumor Diameter
- ◉ < 3 cm
- ○ >= 3 cm

T Category
- ◉ Ta
- ○ T1

Grade (WHO 1973)
- ◉ G1
- ○ G2
- ○ G3

Concomitant CIS
- ◉ No
- ○ Yes

[Calculate Probabilities] [Clear] [Exit]

	1 Year	2 Years	3 Years	4 Years	5 Years
Probability of Recurrence	0.38	0.51	0.56	0.59	0.62
Probability of Progression	0.01	0.03	0.04	0.05	0.06

Reference: Sylvester RJ, van der Meijden APM, Oosterlinck W, Witjes JA, Bouffioux C, Denis L, Newling DWW, Kurth KH. Predicting recurrence and progression in individual patients with stage Ta T1 bladder cancer using EORTC risk tables: A combined analysis of 2596 patients from 7 EORTC trials. European Urology 49: 466-477, 2006.

Programmed by Richard Sylvester, EORTC Data Center, 83 avenue Mounier, 1200 Brussels, Belgium.

Version 1.0, January 2006

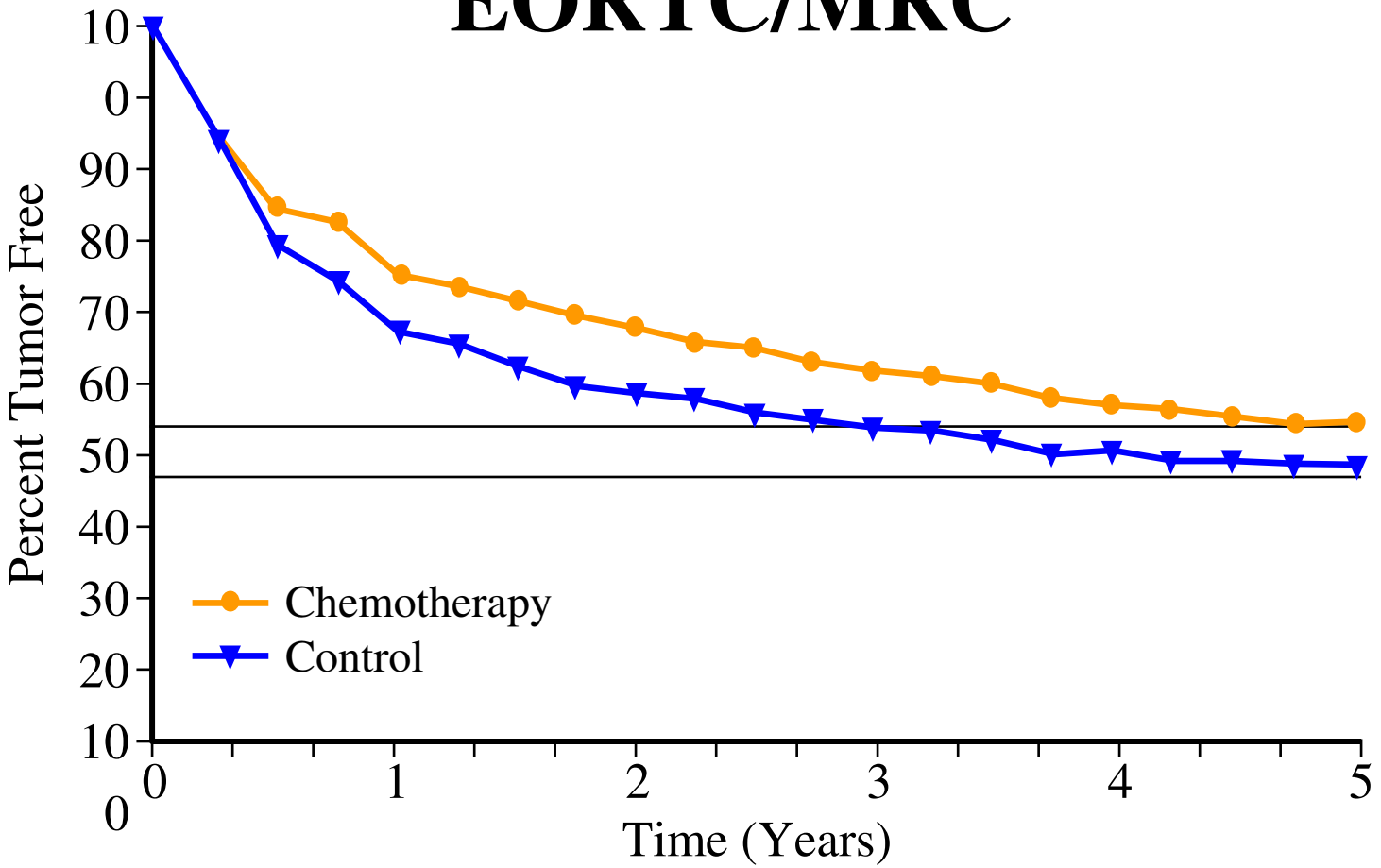
http://www.eortc.be/tools/bladdercalculator/

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

5 year Tumor Recurrence Curves With Chemotherapy vs Control

EORTC/MRC



Intravesical Chemotherapy Principles:

- ***Direct contact*** required
- Kill α drug concentration & duration of exposure
- Optimal response occurs with treatment within 6 hours of tumor resection
- Significant improvement with continued treatment or maintenance is difficult to demonstrate
- Low-grade tumors respond best

Improved Mitomycin C Chemotherapy

Au J: J NCI. 93:597-604, 2001

- 230 randomized Ta, T1 pts.
- ***Standard*** MMC, 20mg/20cc weekly x6 vs. ***Optimized*** MMC: 40mg/20cc, NPO overnight, ultrasound confirmed empty bladder, and alkalinization with 1.3gm $NaHCO_3$
- 5 yr recurrence free: ***Standard*** 24.6% versus 41% with ***Optimized*** MMC; time to recurrence increased from 11.8 to 29.1 months ($P<0.005$)

My Recommendation for Ta, T1 TCC

- A Single postop chemotherapy instillation is sufficient for low grade TCC:
  - Thiotepa 30mg/15cc
  - Mitomycin 40mg/20cc
  - Doxorubicin (Adria) 50mg/25cc

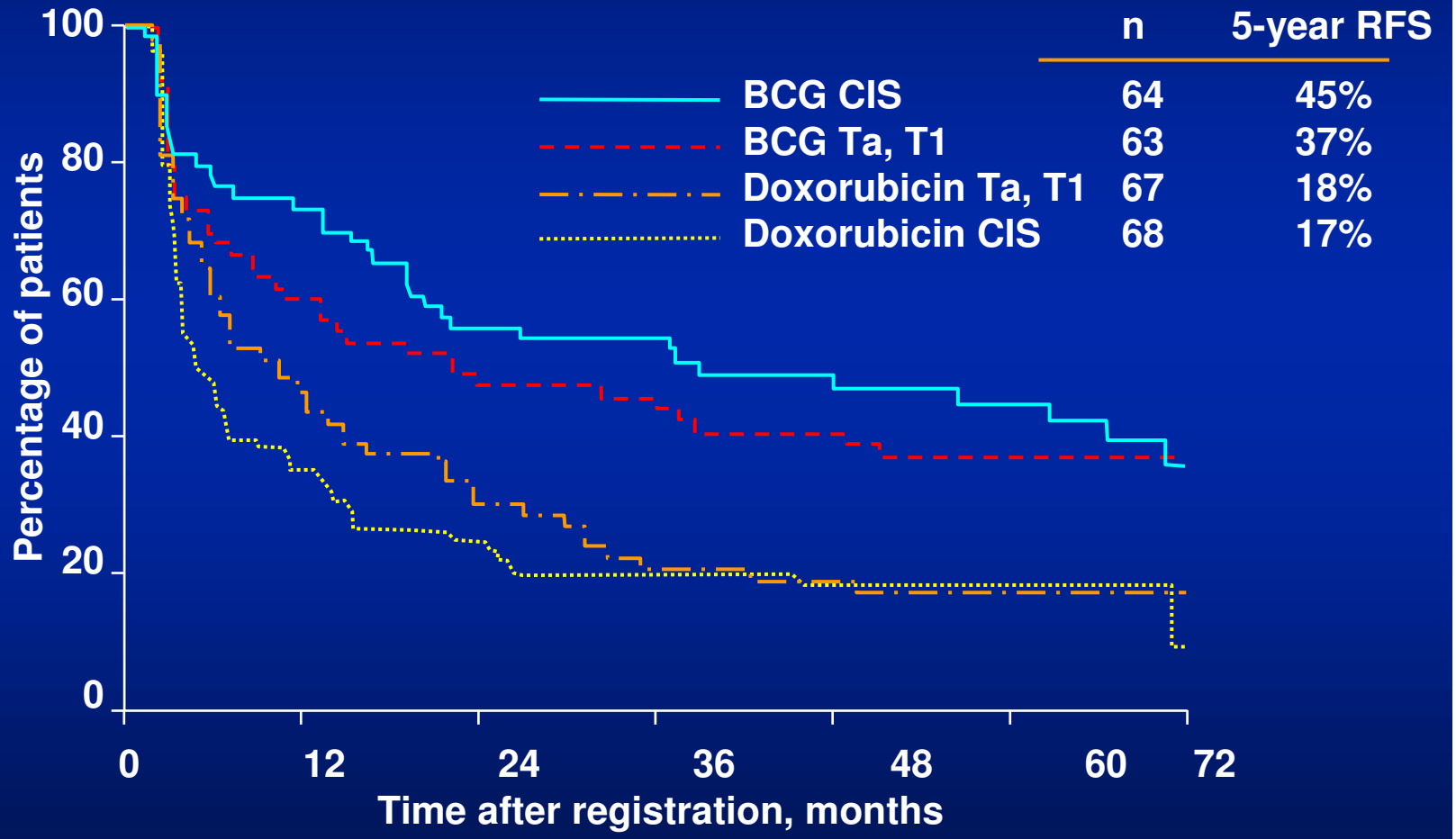
  Each held for 30 minutes.
- Never give MMC or Adriamycin with perf. 56 to 58% of postop cytograms show reflux!*
- Thiotepa can (should?) be given with perf.
- Never give BCG immediately postop!

* Hayek OR, AUA 2007 abstract 338

Risk Groups
Improve Treatment Selection

- Low Risk: Low Grade (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**

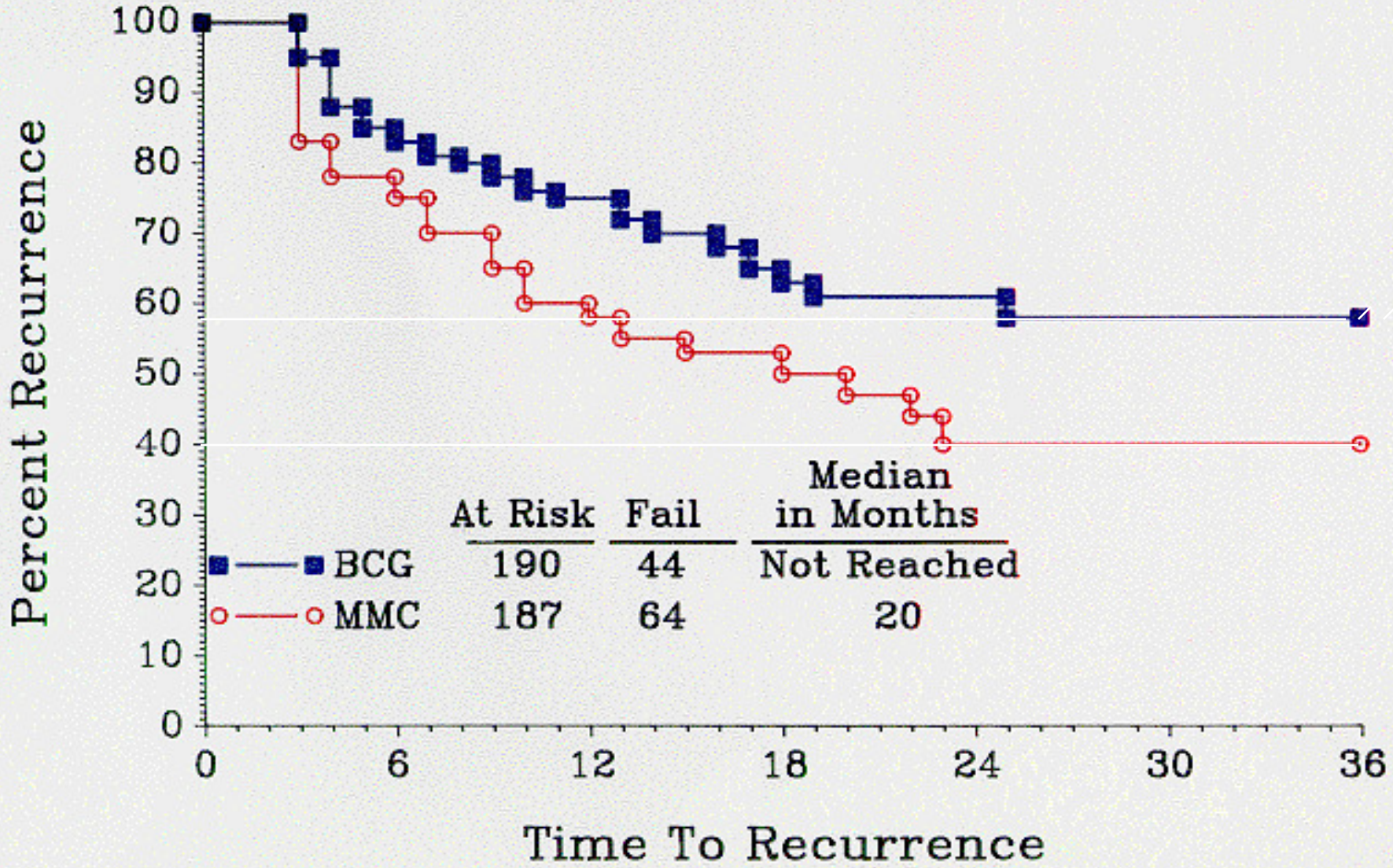
BCG Versus Doxorubicin: Time to Treatment Failure



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

BCG Versus Mitomycin–C (SWOG 8795)

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



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.

Management of Recurrence

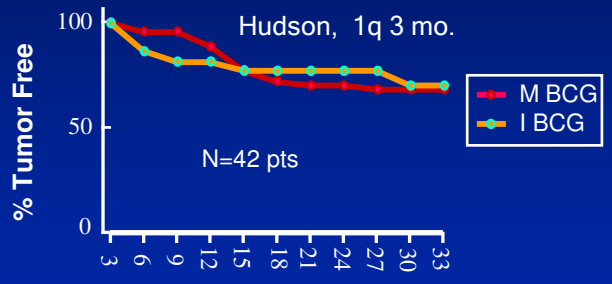
- Definition of failure:
  - Recurrence after treatment?
  - Early (one year) recurrence after chemo?
  - Late (6 or more months) recurrence after BCG induction or recurrence on 3 week maintenance?
- Chemo failures: BCG appropriate for even for low grade, TA, but long term maintenance may not be indicated.
- BCG Failures: Chemo, repeat BCG, BCG IFn, and novel or experimental therapies

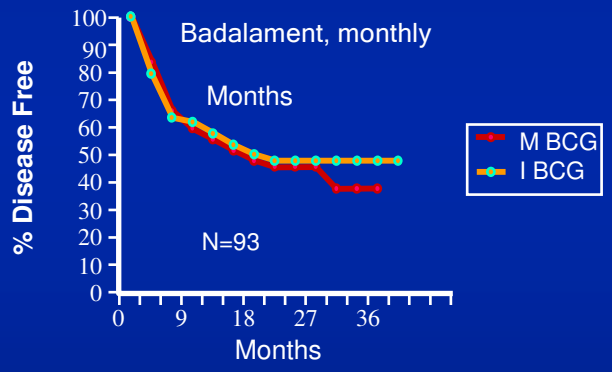
Second Induction Course of BCG

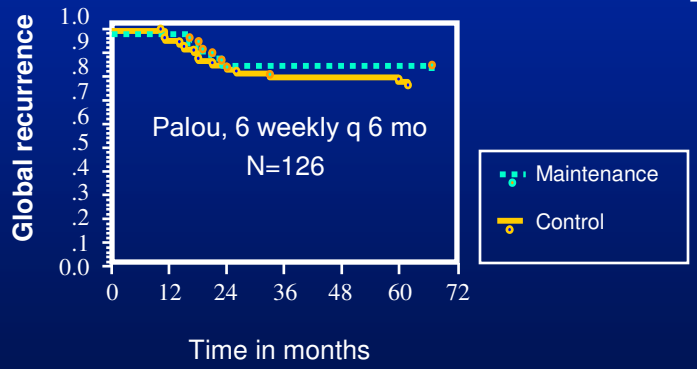
Author	N	R	R%	TTR
Bretton	28	18	64%	21 mo
Hurle	13	6	46%	27 mo
Kohjimoto	16	6	38%	35 mo
Yamada	31	20	64%	36 mo
Bui	11	6	54%	84 mo
O'Donnell	40	19	47%	26 mo*
Nadler	66	39	59%	45 mo
Total:	205	114	56%	21-84 mo

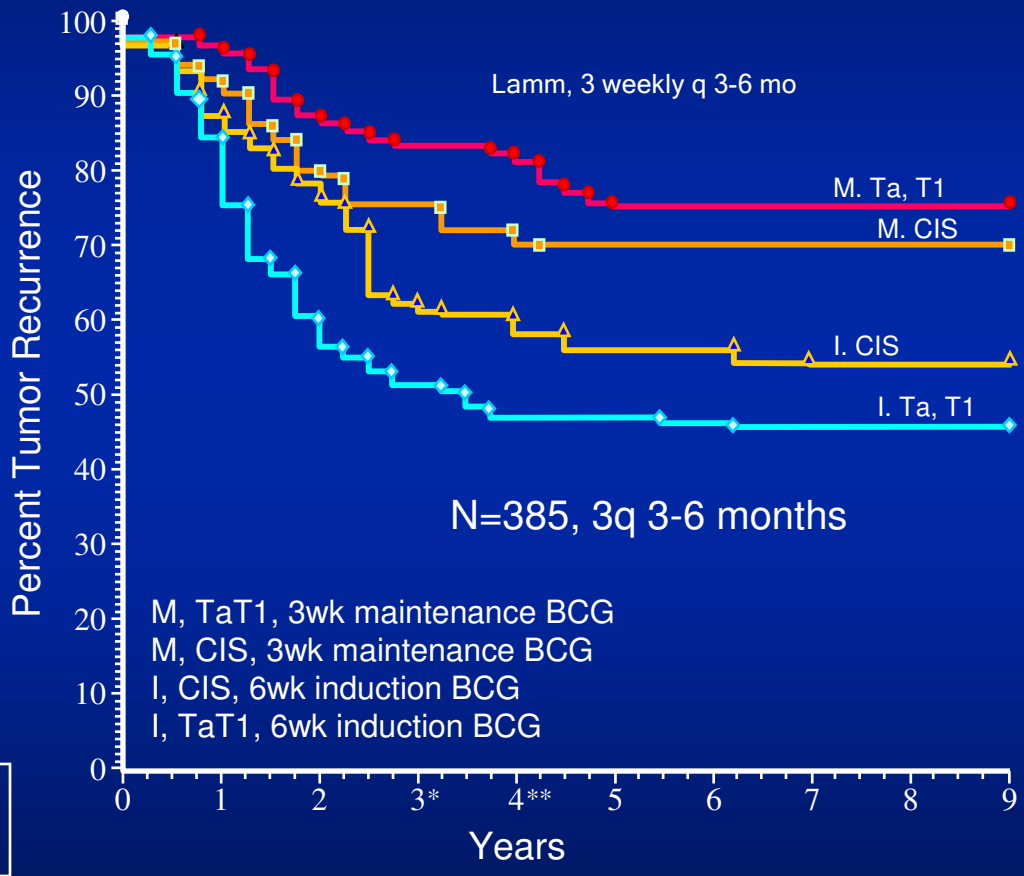
*BCG plus interferon: 53% recurrence free 26 m.
vs 36% free (21-84 m) without Ifn

BCG Maintenance: Not Created Equal





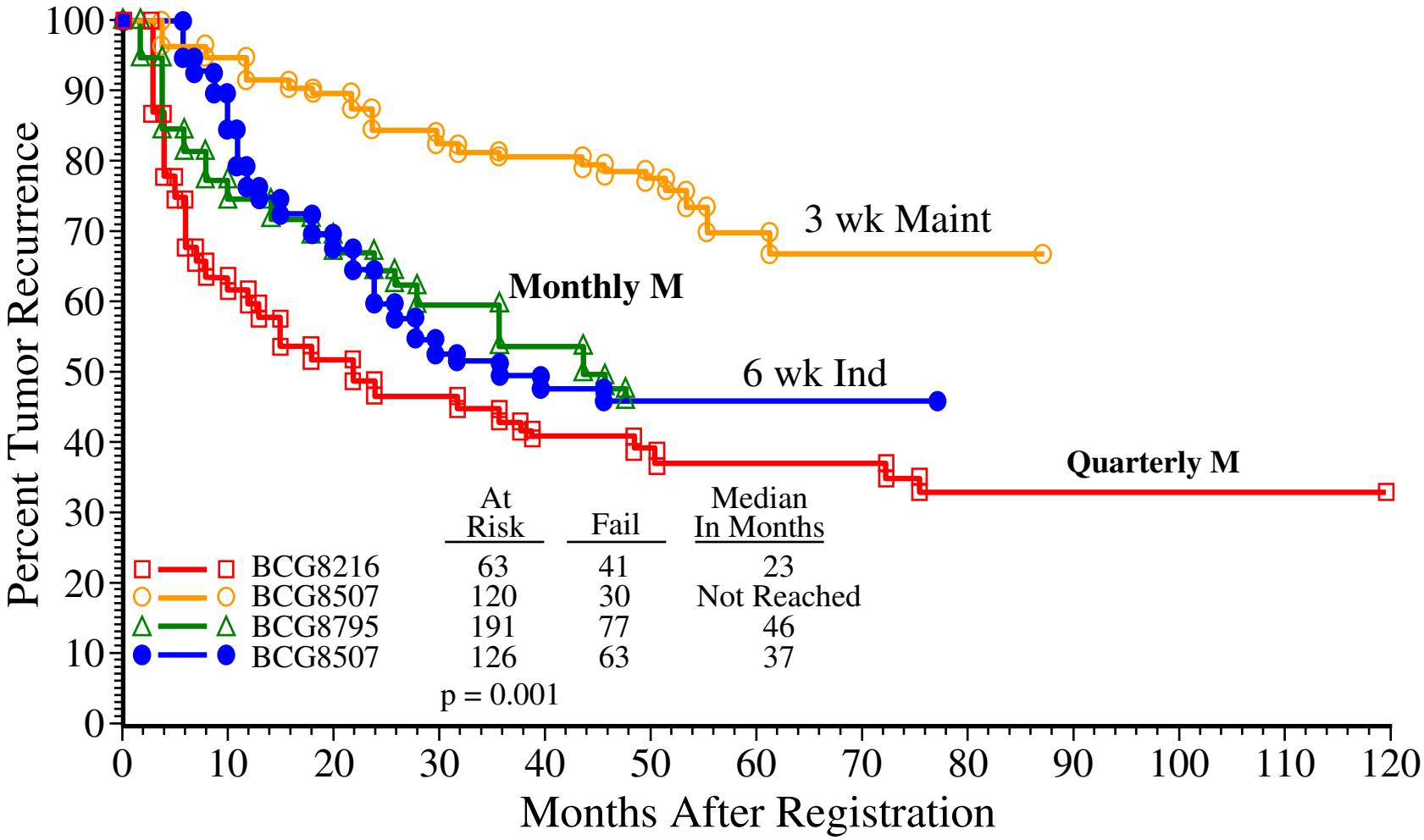




* Completion of Therapy
* Apparent Increase in Rate of Recurrence
** One Year After Completion of Maintenance

SWOG BCG Arms

Papillary Patients Only

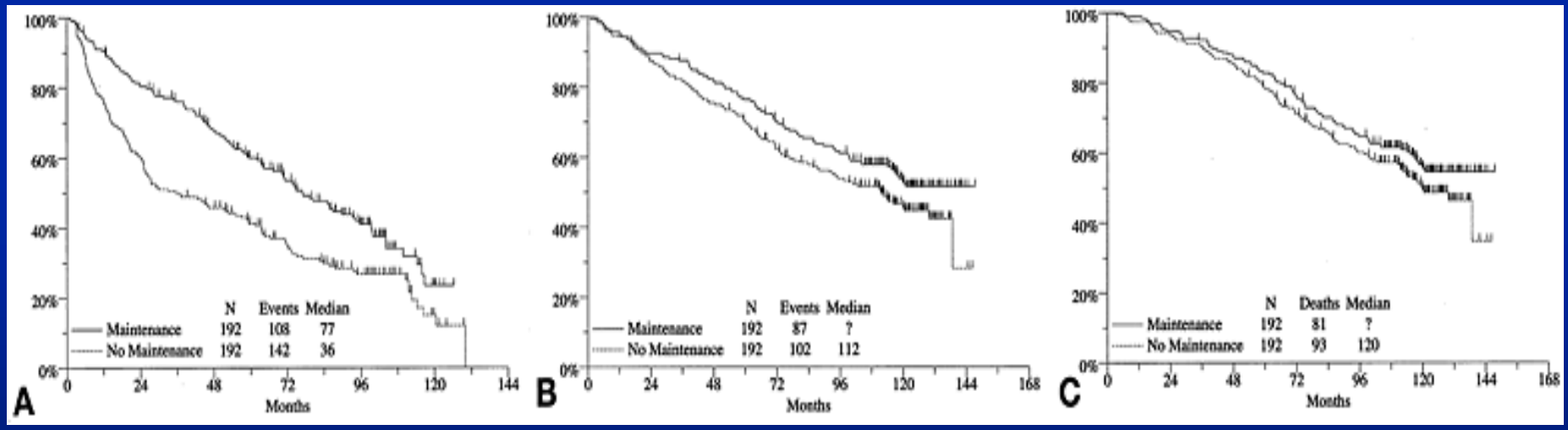


3 Week Maintenance BCG

Recurrence -free Survival

Worsening -free Survival

Survival



p < 0.0001

p = 0.04

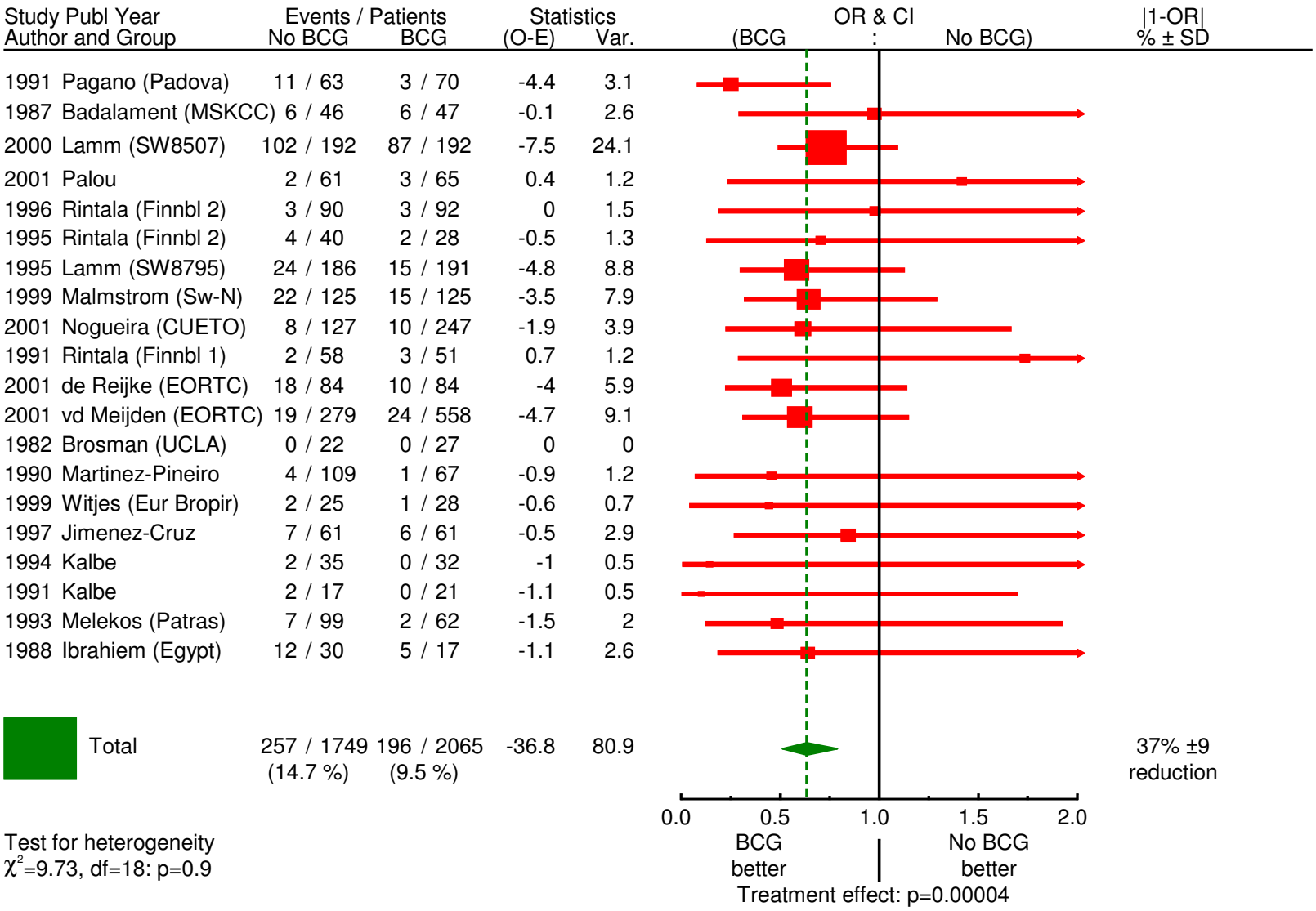
p = 0.08

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

Can BCG Delay or Prevent Progression in Superficial Bladder Cancer ? Sylvester R: J Urol. Nov., 2002

- Meta-analysis of 24 studies, 4863 patients randomized to BCG vs surgery alone (2), BCG maintenance (3), chemotherapy (14), or other immunotherapies (5).
- 2.5 year median follow (max 15)
- 82% Ta, T1, 37% G1, 55% G2, 8% G3; 18% CIS
- 78% received maintenance BCG, 10-30 Rx over 18 weeks to 3 yrs.

Progression
All Studies With Maintenance



Test for heterogeneity
χ^2=9.73, df=18: p=0.9

Early Cystectomy for G3,T1 TCC?

- Survival of patients who come to cystectomy after failing BCG is markedly reduced, *therefore G3,T1 patients should be treated with cystectomy rather than BCG!(?)*
- 40% undergoing immediate cystectomy have T2 or greater disease, ~50% of whom will survive 5 years **(20% 5 yr mortality).**
- With 88% progression free on BCG at 5 years, if 100% of those progressing died following cystectomy **(12% 5 yr mortality),** survival would still be ***better*** *(88% versus 80)% than immediate cystectomy!*

Understaging of High-Risk T1 Bladder Cancer

Study		% Understaged
Pagano	(1991)	35%
Amling	(1994)	37%
Soloway	(1994)	36%
Freeman	(1995)	34%
Ghoneim	(1997)	62%
Herr	(1999)	49%
Dutta	(2001)	46%
Overall Average:		43%

BCG in Grade 3, Stage T1 TCC

Author	No.	Progression (%)	Followup (mos)
Boccon Gibod '89	47	12	
Dal Bo '90	24	25	22
Samodi '91	62	0	46
Cookson '92	16	19	59
Eure '92	30*	7	39
Pfister '95	26	27	54
Hurle '96	51	14	33
Zhang '96	23	35	45
Serretta '96	50	12	52
Vicente '96	95	11	46
Lebret '98	35	12	45
Baniel '98	78	8	56
Klan '98	109	13	78
Gohji '99	25	4	63
Brake '00	44	16	43
Pansadoro '02	81	15	76
Total:	796	12	

BCG Rx G3, T1

- 785 pts superficial TCC, 1982-2000
- 11% (86) G3, T1 treated with maintenance BCG
- **91 month follow up**
- Recurrence: 35%, @ mean of 29 months
- **Progression: 14%, @ mean of 16 months**
- Cancer mortality: 6%, 71 month median follow
- Cystectomy: 9%; 70% alive with intact bladder
- "Cystectomy should not be considered for first line Rx"

Pansadoro V: J Exp Clin Cancer Res. 2003;22:223-7.

Cystectomy or BCG for T1G3?

- 86 pts with **T1** TCC treated with BCG and followed for 59 (9-149) months.
- 31% early recurrence, but 91% overall disease free with additional BCG.
- **Progression to T2 or higher: 7%**
- Disease specific survival: 85/86=99%

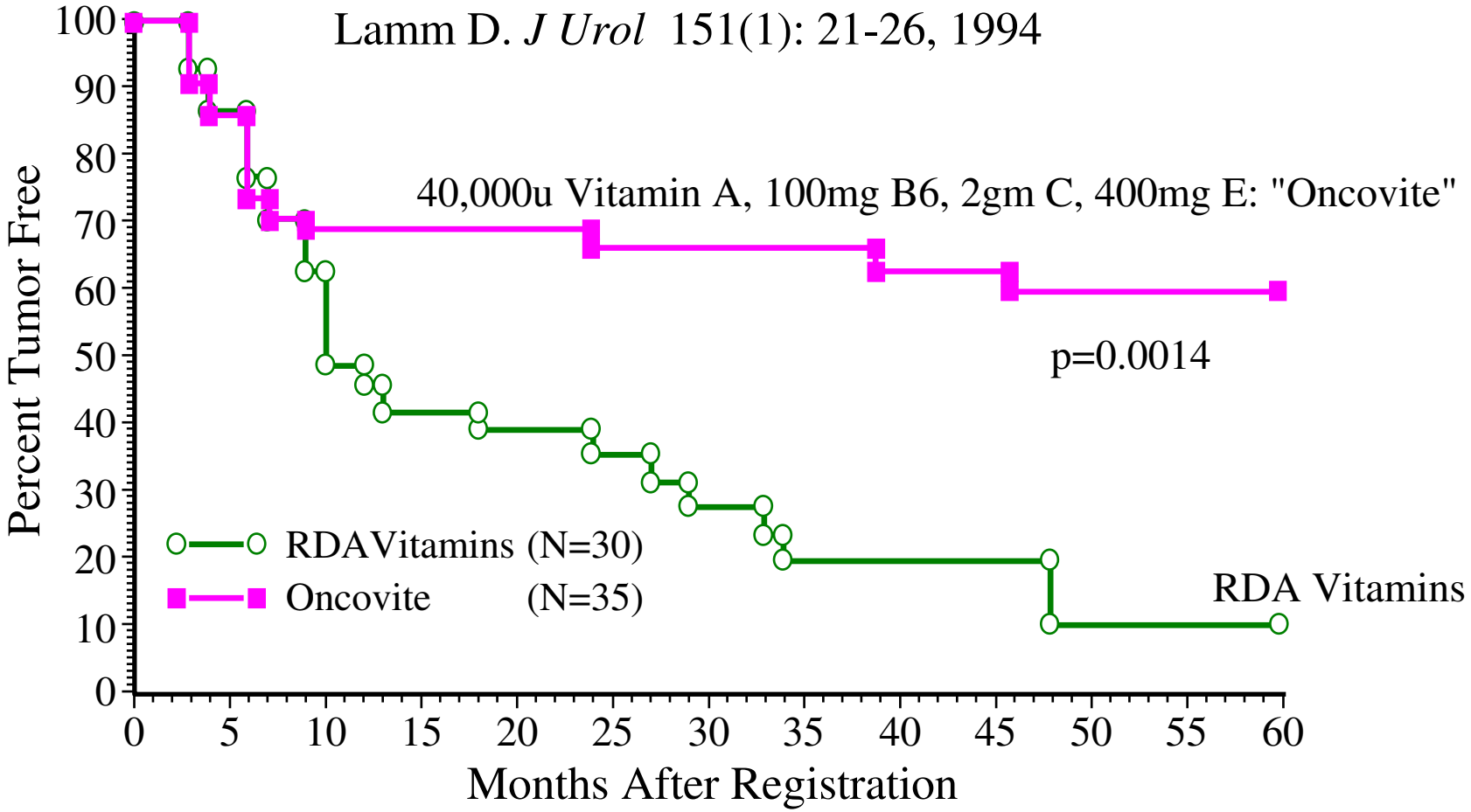
Cookson MS: J Urol. 1992;148:797-801. UT San Antonio

Future Therapies

- New treatments are much needed!
- FDA problem: new treatments compared with BCG or BCG refractory
- What's new: alternative therapy, combo chemo, electomotive /hyperthermic chemo, new/combined IRx

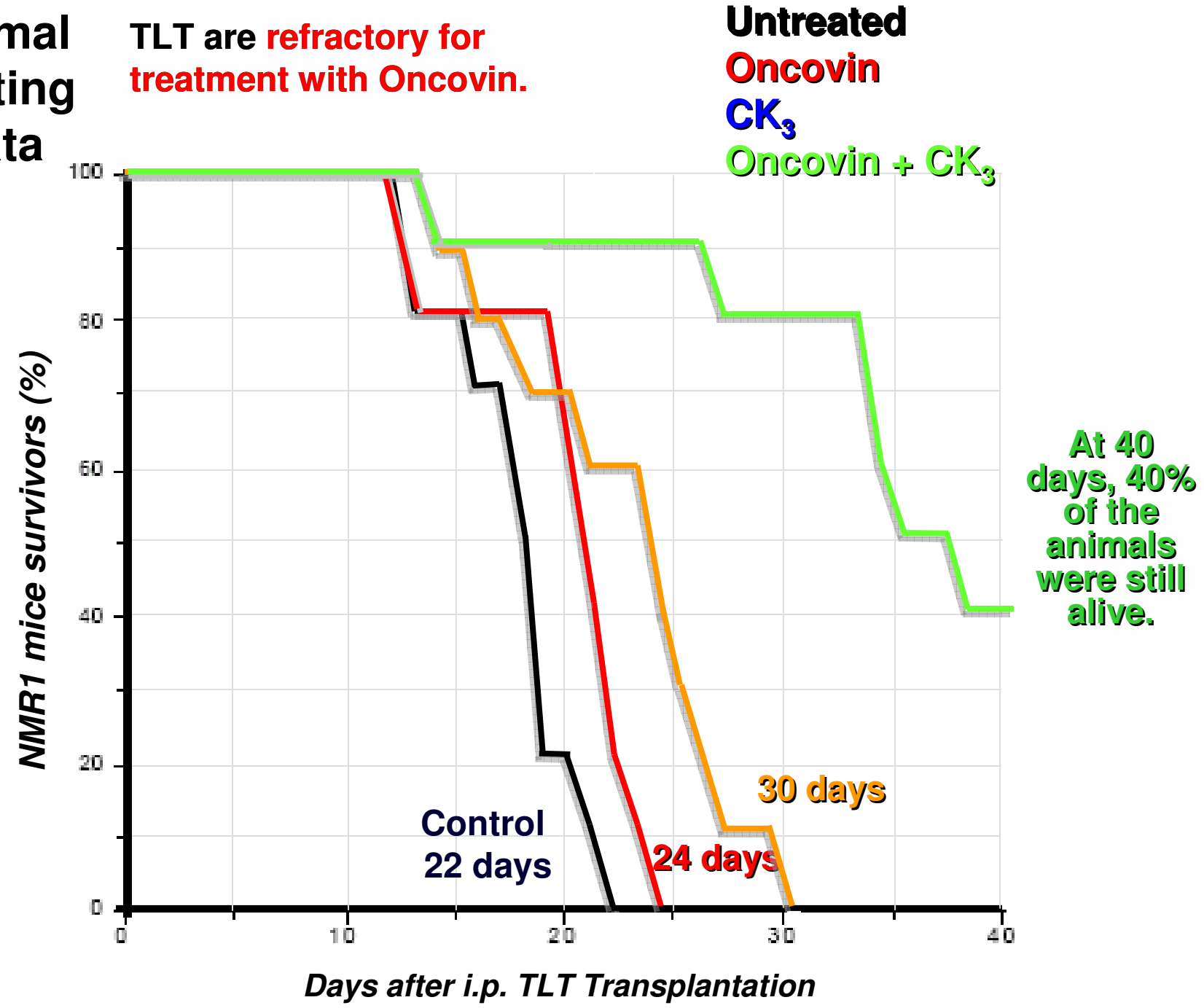
Kaplan Meier Estimate of 5 Year Tumor Free Rate

In Patients Receiving Vitamin Supplement and BCG Therapy For Bladder Carcinoma

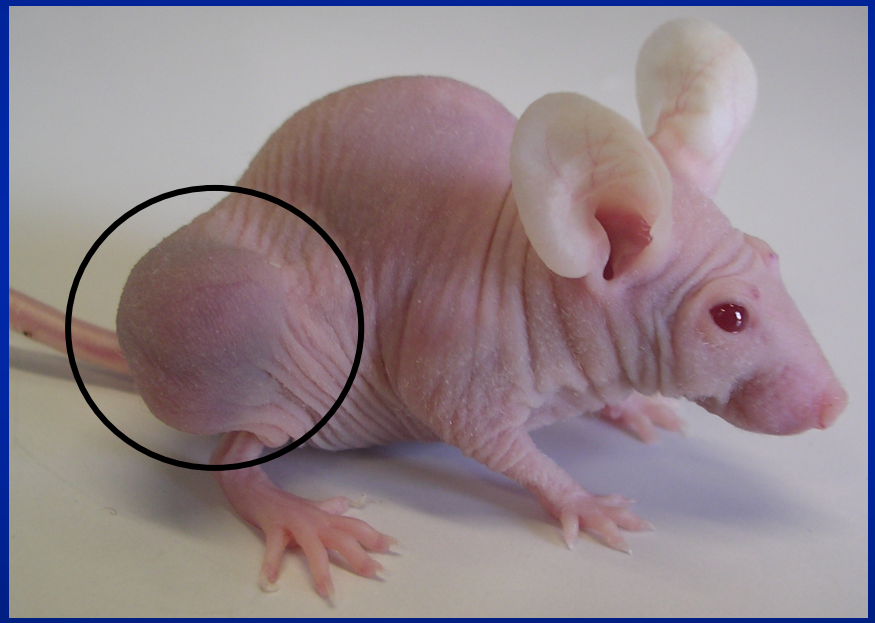


Animal Testing Data

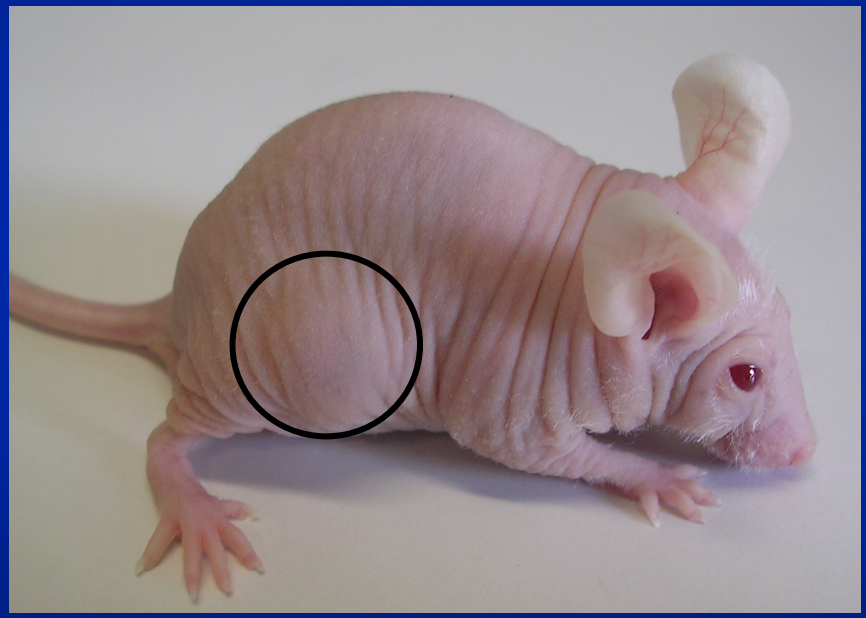
TLT are refractory for treatment with Oncovin.



CK_3 Single injection murine monotherapy - K652 (human CML)cell line



Untreated



Single treatment 4 weeks later

One injection reduced tumor volume 60-65%

Fluorescence Cystoscopy

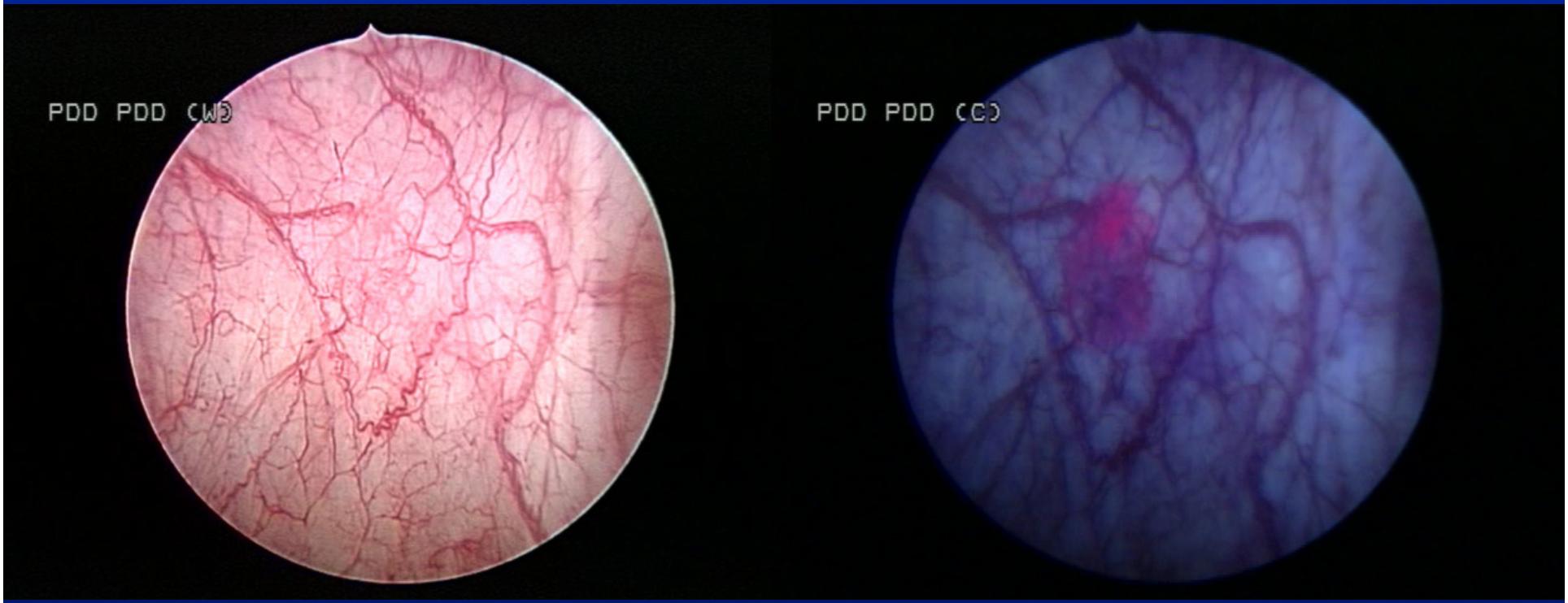
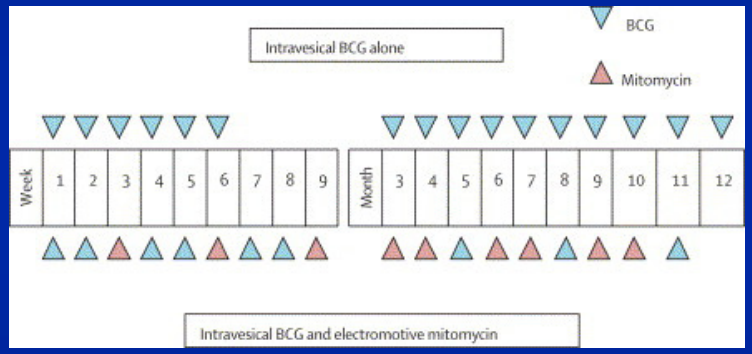
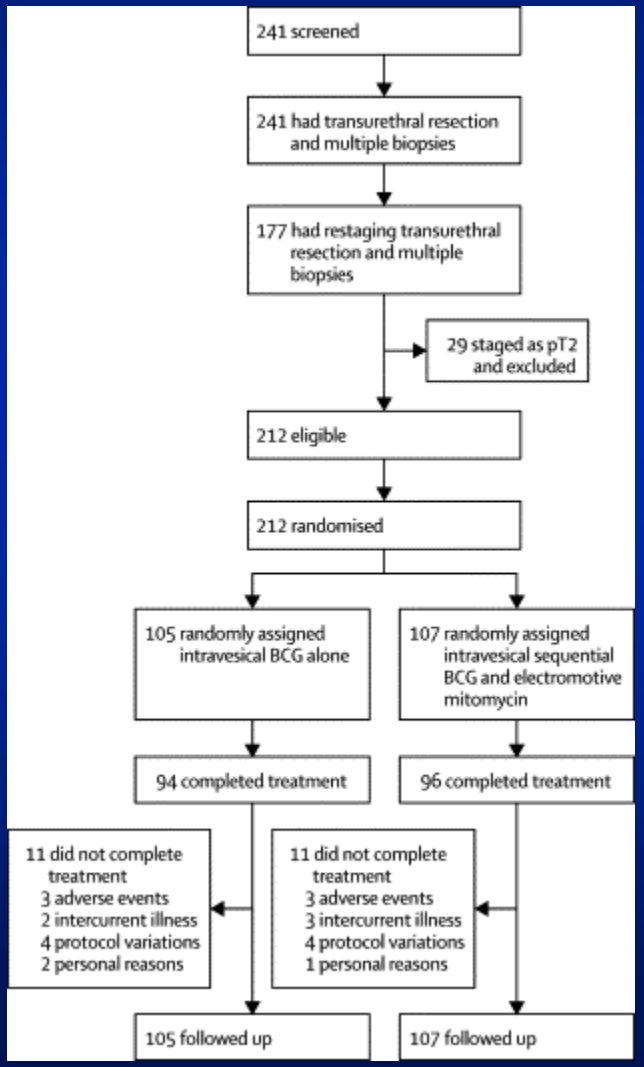


Photo by Bart Grossman, 2006

BCG & Electromotive Mitomycin

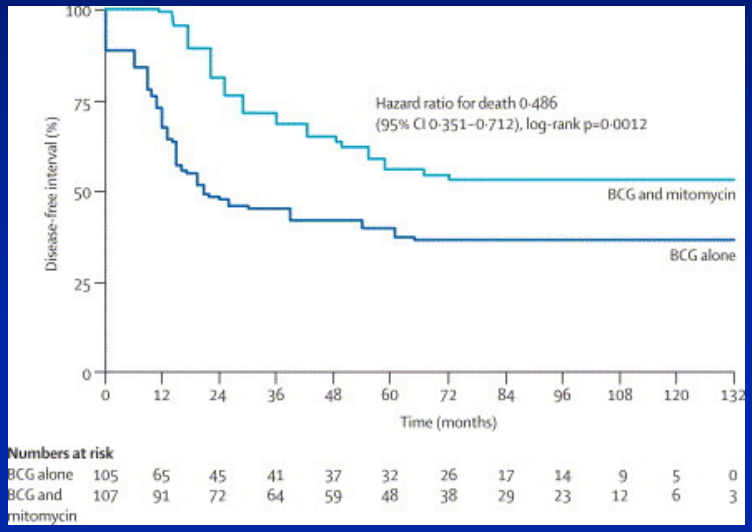




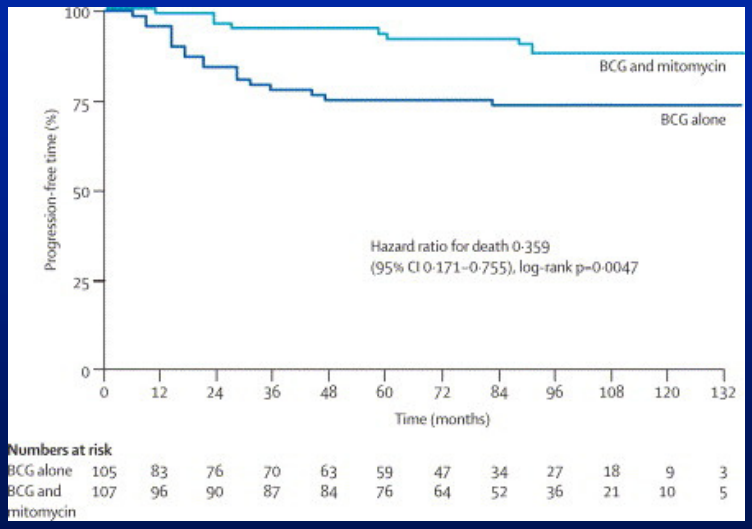
Di Stasi SM, et al. *Lancet Oncol.* 2006;7:43-51.

Slide courtesy of Bart Grossman, MD Anderson

BCG & Electromotive Mitomycin



Disease-free Survival

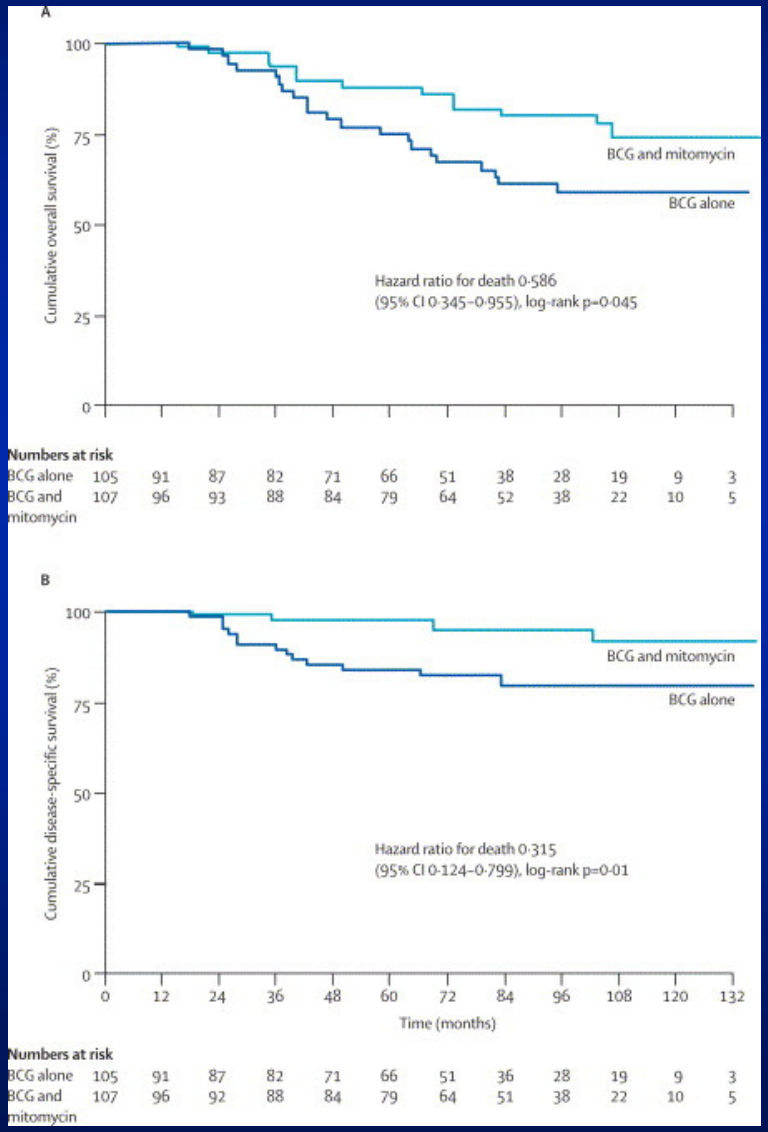


Progression-free Survival

Di Stasi SM, et al. *Lancet Oncol.* 2006;7:43-51.

Slide courtesy of Bart Grossman, MD Anderson

BCG & Electromotive Mitomycin



Overall Survival

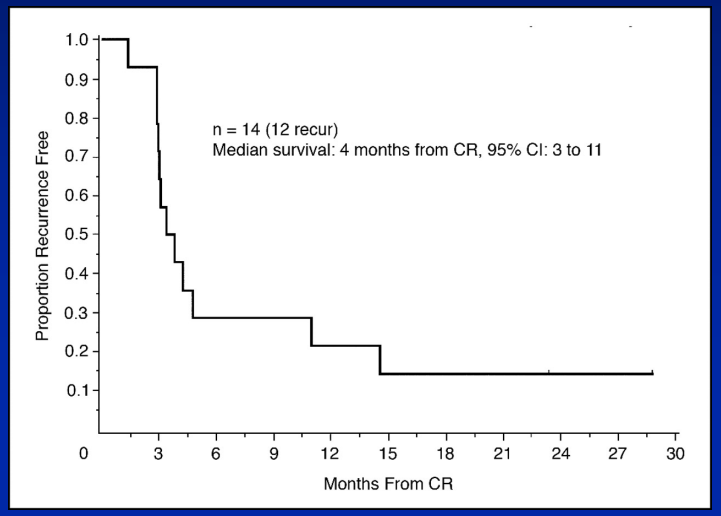
Disease-specific Survival

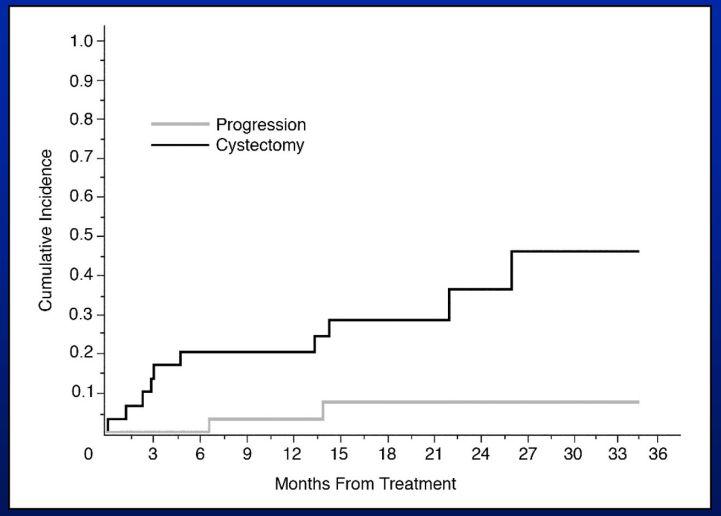
Di Stasi SM, et al. *Lancet Oncol.* 2006;7:43-51.

Slide courtesy of Bart Grossman, MD Anderson

Gemcitabine

- N = 30
- BCG Refractory or Intolerant
- 2 courses 2 g/100 mL twice weekly for 3 weeks separated by 1 week of rest





Dalbagni G, et al. *J Clin Oncol*. 2006;24:2729-2734.

Slide courtesy of Bart Grossman, MD Anderson

Other Drugs

- **Docetaxel (Taxotere)**
  - **N= 18**
  - **56% short-term DFS**
  - **75 mg/100 mL well-tolerated (2 hours)**
  - **No systemic absorption**
  - **McKiernan JM, et al. *J Clin Oncol*. 2006;24:3080-3075.**
- **Apaziquone (Eoquin)**
  - **N =46, marker lesion study**
  - **CR in 30 (65%)**
  - **4 mg/40 mL (1 hour)**
  - **Van der Heijden AG, et al. *J Urol.* 2006;176:1349-1353.**

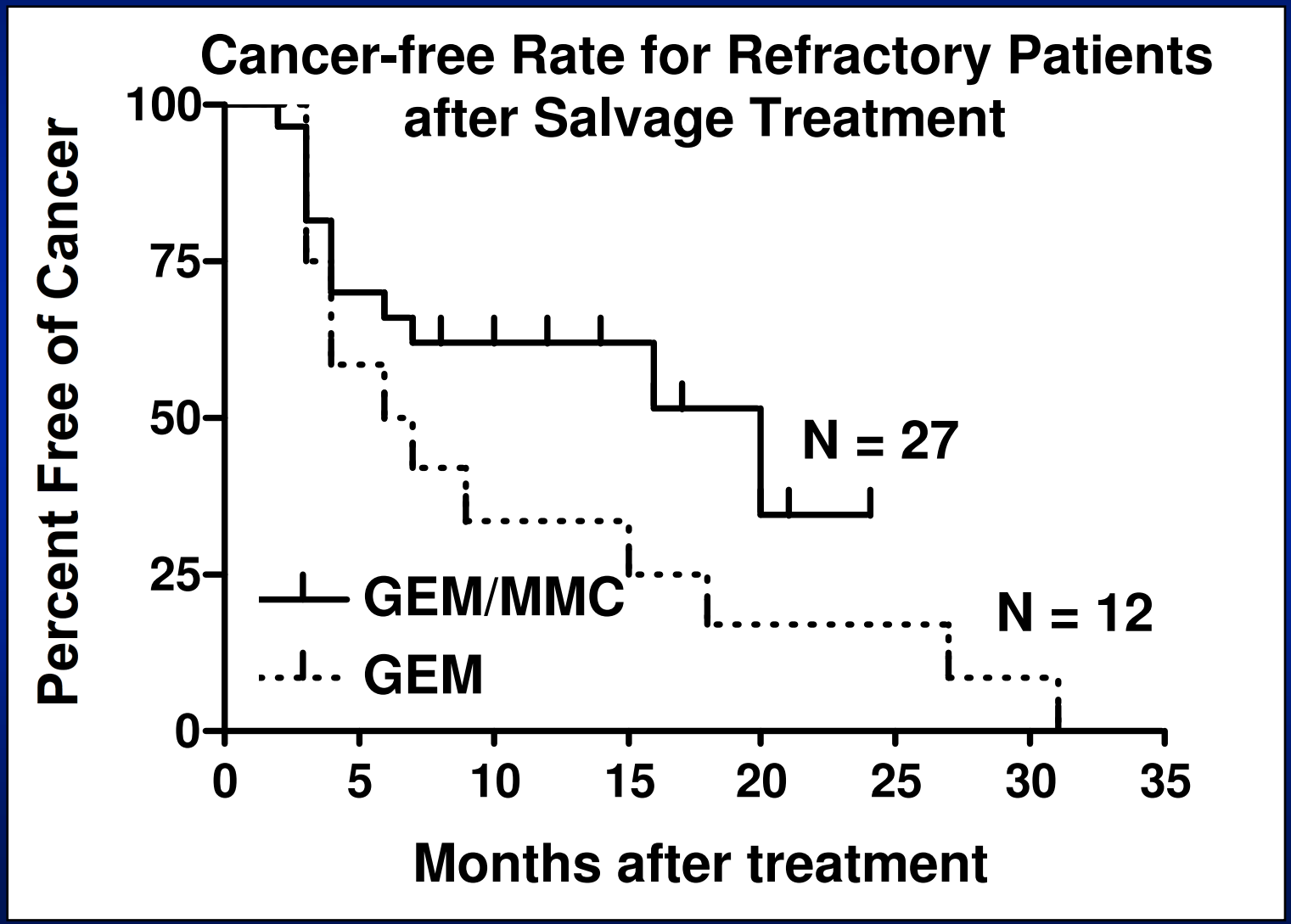
Slide courtesy of Bart Grossman, MD Anderson

Multi-Agent Intravesical Chemotherapy

- Multidrug regimens: nearly always better in advanced TCC
- Combine to increase cell kill without increased toxicity
- Most frequent DLT for intravesical chemotherapy is cystitis
- Combine drugs with differing mechanisms of action, one or more without vesicant (irritative) side effects

Mike O'Donnell, 2006

UIHC Experience w/ BCG + IFN Failures
'06 AUA 840 (Maymi)



Alternative Immunotherapy

- KLH: 59% reduction in tumor recurrence with ***systemic*** administration alone!
- MCC/Regressin/Mycobacterium phlei cell walls: effective in CIS and BCG failures.
- BCG Interferon: 60% protection from recurrence in BCG failure patients.
- Others?

Gene/DNA Therapy

- CG0070: Cell Genesys Rb/GMCSF modified Adenovirus: Phase 1-2
- Schering: promising IFn producing agent
- Biocancel: H19 in clinical trials

Conclusions

- Surgery Counts! Extend resection, send margin, then roller-balling base and edges (?); or re-resect
- Immediate postoperative chemotherapy: standard
- **Concentrated** chemo for low risk, BCG for high
- **3 week maintenance BCG**, not repeated 6 weeks
- High grade: carefully follow upper tracts and prostate. Low threshold for TURP.
- New treatments are greatly needed. Let Andy know and support research.
- **BCGOncology.com** for slides, handout, questions.

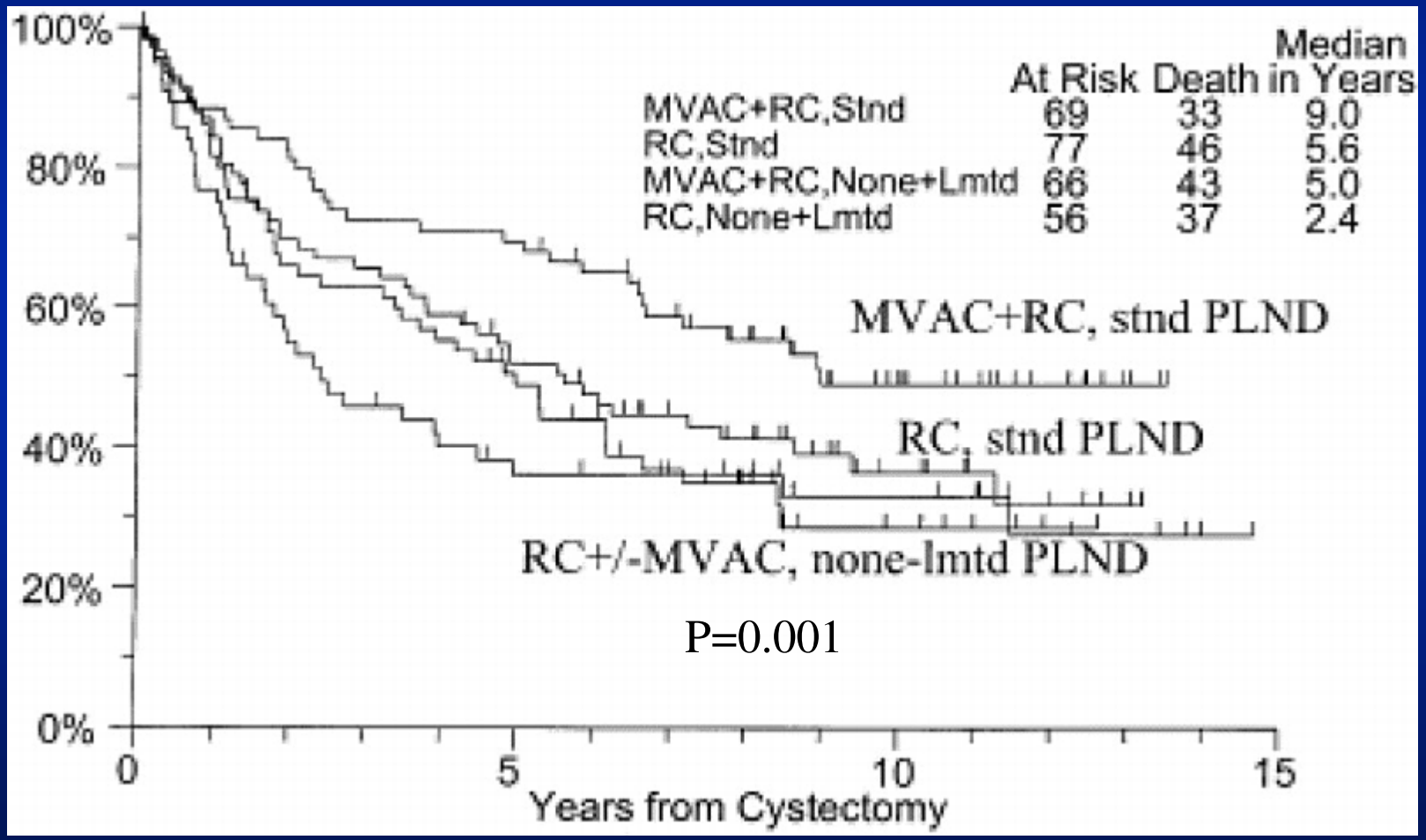
Thanks

For Your Attention!

Extra credit slides follow

PLND and MVAC Improve Survival

Herr HW: JCO, 2004 172:1286



5 yr survival with MVAC plus PLND 52% vs 34% with inadequate or no PLND

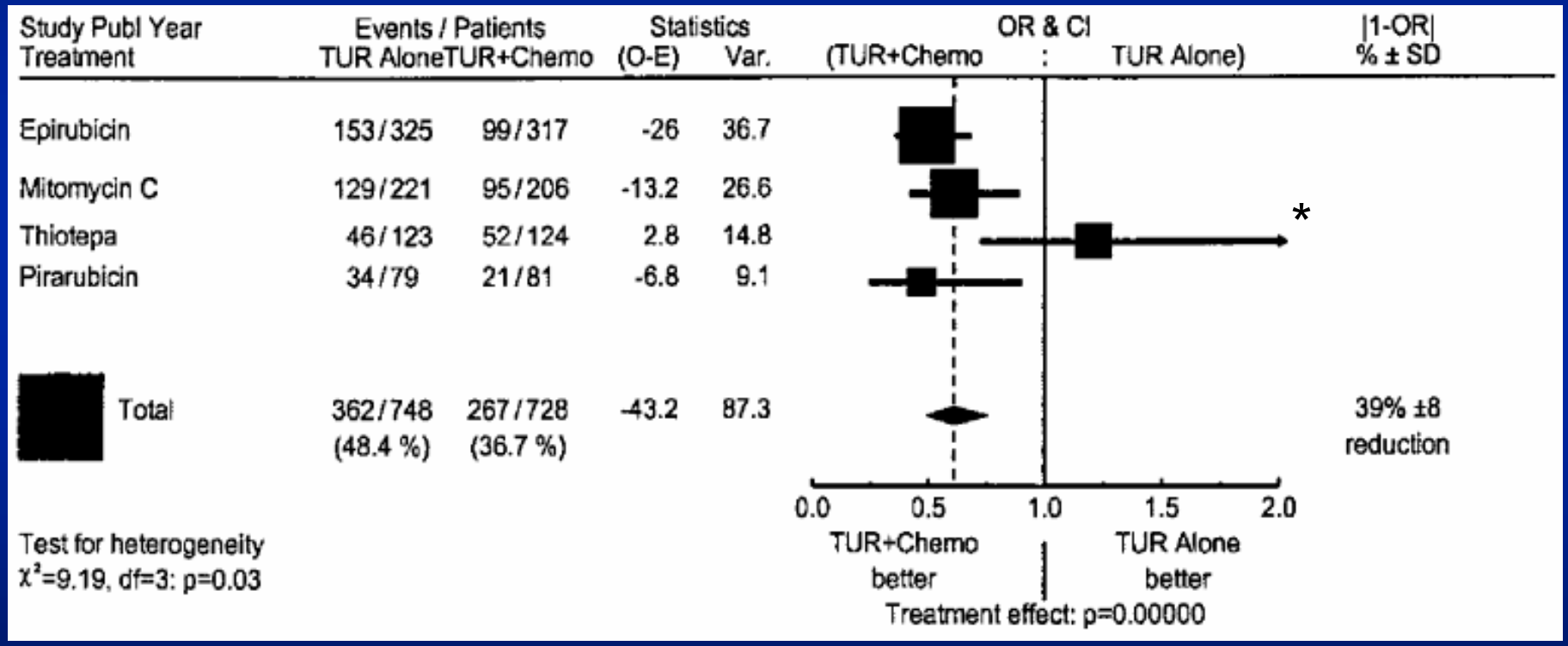
Improved Mitomycin C Chemotherapy

Au J: J NCI. 93:597-604, 2001

- 230 randomized Ta, T1 pts.
- ***Standard*** MMC, 20mg/20cc weekly x6 vs. ***Optimized*** MMC: 40mg/20cc, NPO overnight, ultrasound confirmed empty bladder, and alkalinization with 1.3gm $NaHCO_3$
- 5 yr recurrence free: ***Standard*** 24.6% versus 41% with ***Optimized*** MMC; time to recurrence increased from 11.8 to 29.1 months ($P<0.005$)

Perioperative Chemotherapy

Forest Plot of Recurrence



* Thiotepa study included dilute, ineffective preparation

Sylvester RJ, et al. *J Urol.* 2004;171:2186-2190.

Meta-Analysis: Immediate Postoperative Intravesical Chemotherapy

- 1476 patients in 7 randomized clinical trials
- Tumor recurrence reduced from 48.4% to 36.7% (OR 0.61, P<0.0001)
- **Effect may be less in multiple than solitary tumors: 65.2% versus 35.8% recurrence.**
- Benefit is significant (& cost effective) even in solitary, low-grade tumors.

Sylvester RJ. J Urol. 2004;171:2186-90

Muscle Invasive Optimal Therapy Current Survival with Cystectomy

Author	%T0	%Mort	%5yr: pT2	pT3	pT4
Roehrborn	-	2%	60	33	21
Pagano	9%	2%	63	36	24
Wishnow	5%	1%	57	15	21
Waehre	25	-	79	46	33
Vieweg	8%	2%	61	36	29
Stein	6%	3%	58	22	15
Dalbagni	10	-	72	48	33
Studer	-	4.5%	59	29	25
Grossman	15	0.6	74	52	36
Total: 3,220	12%	2.2%	75	-	28
			67%	35%	27%

Herr HW: J Urol. 2007,177:437

Understaging of High-Risk T1 Bladder Cancer

Study		% Understaged
Pagano	(1991)	35%
Amling	(1994)	37%
Soloway	(1994)	36%
Freeman	(1995)	34%
Ghoneim	(1997)	62%
Herr	(1999)	49%
Dutta	(2001)	46%
Overall Average:		43%

Maier and Baumgartner: J Urol. 141:529, 1989

- 56 pts post TURBT: 28 with 20mg MMC and 28 with MMC plus 200,000 u hyaluronidase
- Schedule: q 2wks x 6 months, then q 4 wks x2yrs
- No increase observed in toxicity and no serum absorption
- 21 mo follow: 9/28 MMC recurrence (32%) verus 2/28 (7%) MMC + hyaluronidase ($P<0.05$)