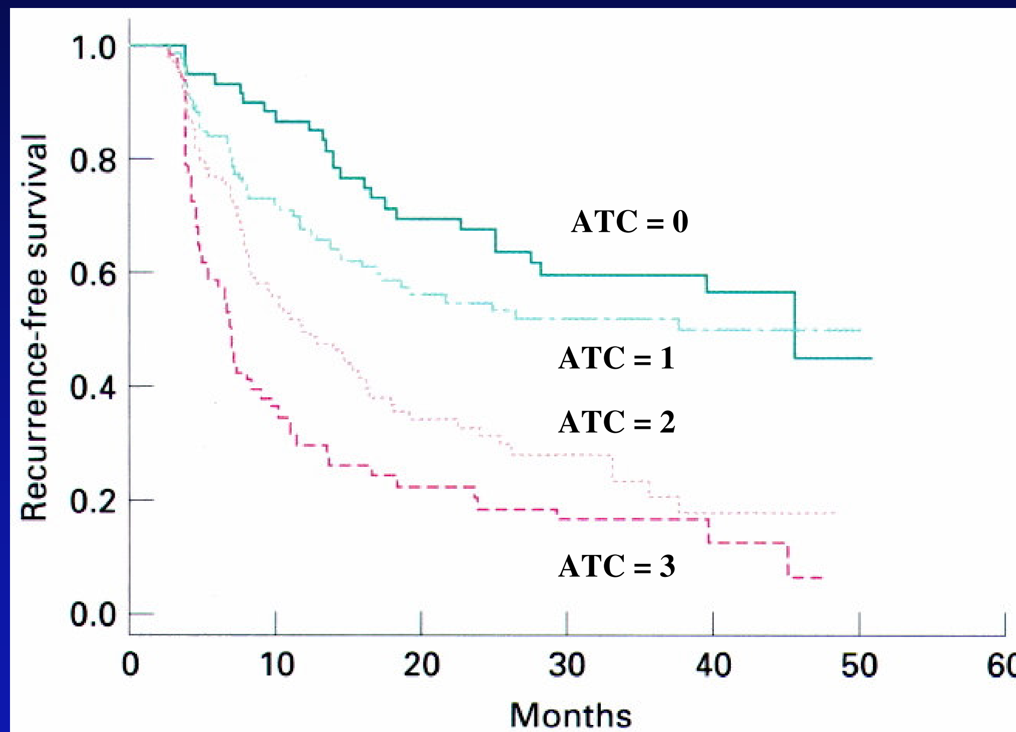
Management of Difficult Cases of Non-Muscle Invasive Bladder Cancer

Bladder Cancer

- Recurrence is common
- Progression is uncommon
- Progression is more important than recurrence
- There are indicators of recurrence and progression

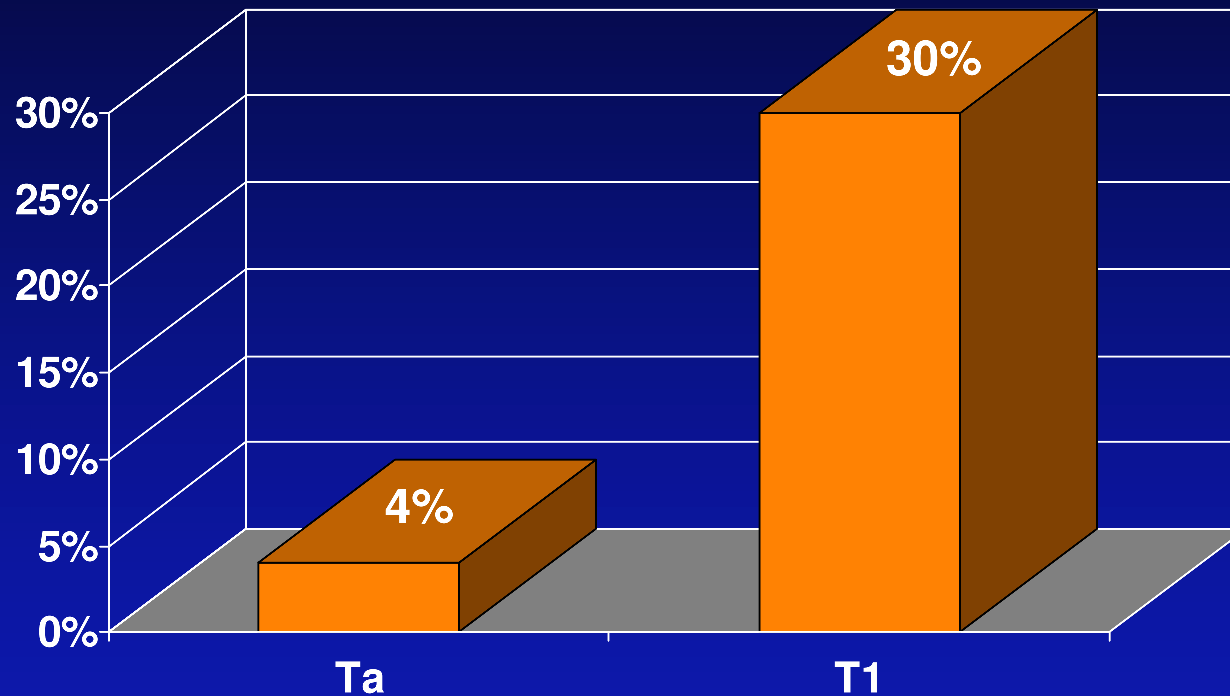
Clinical Prognostic Markers

Risk of recurrence of Ta/T1 TCC by tumor characteristics



Allard et al, Br J Urol 81:692, 1998

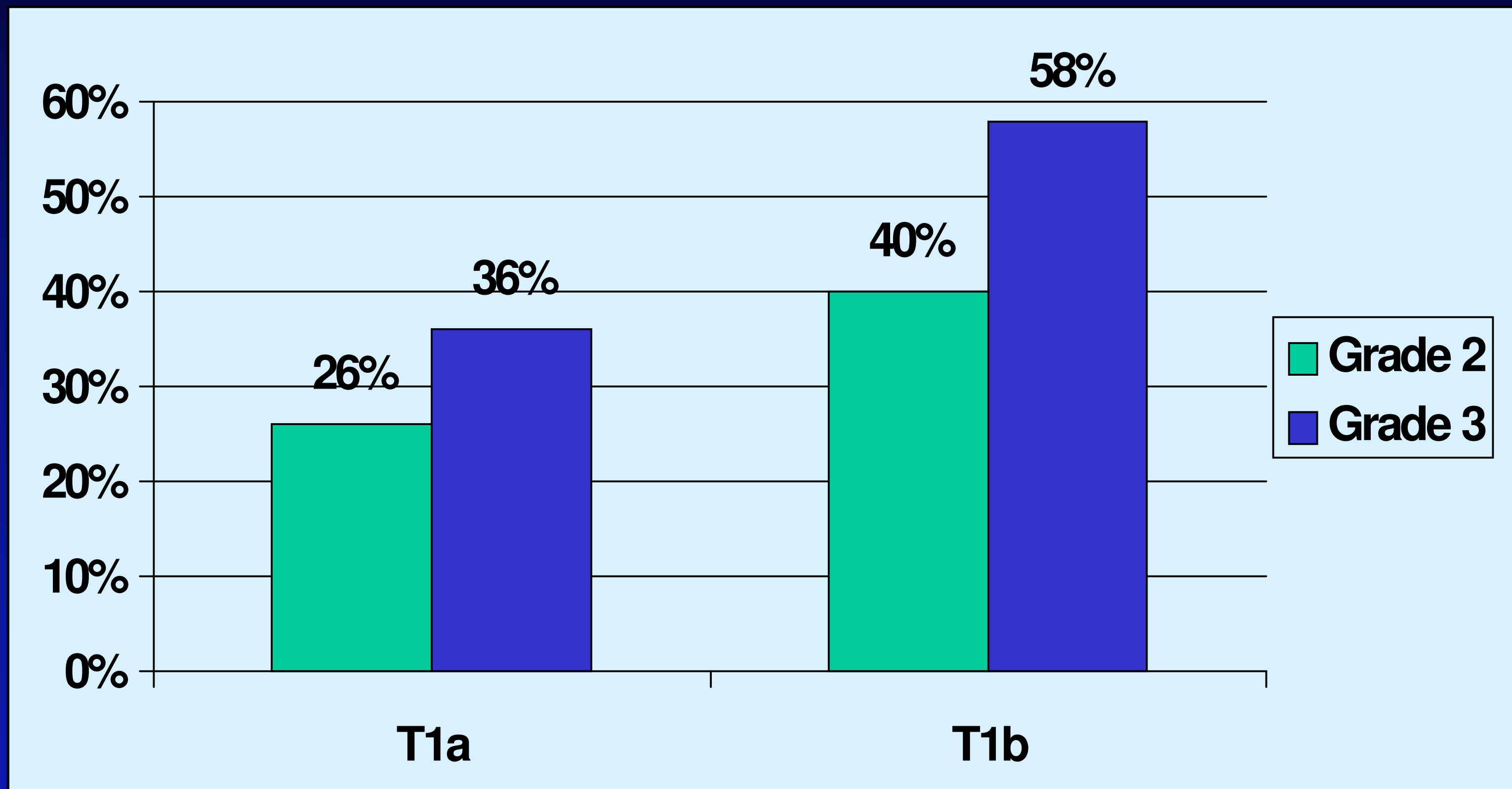
Progression at 3 years after TUR



N = 207
$p < 0.001$

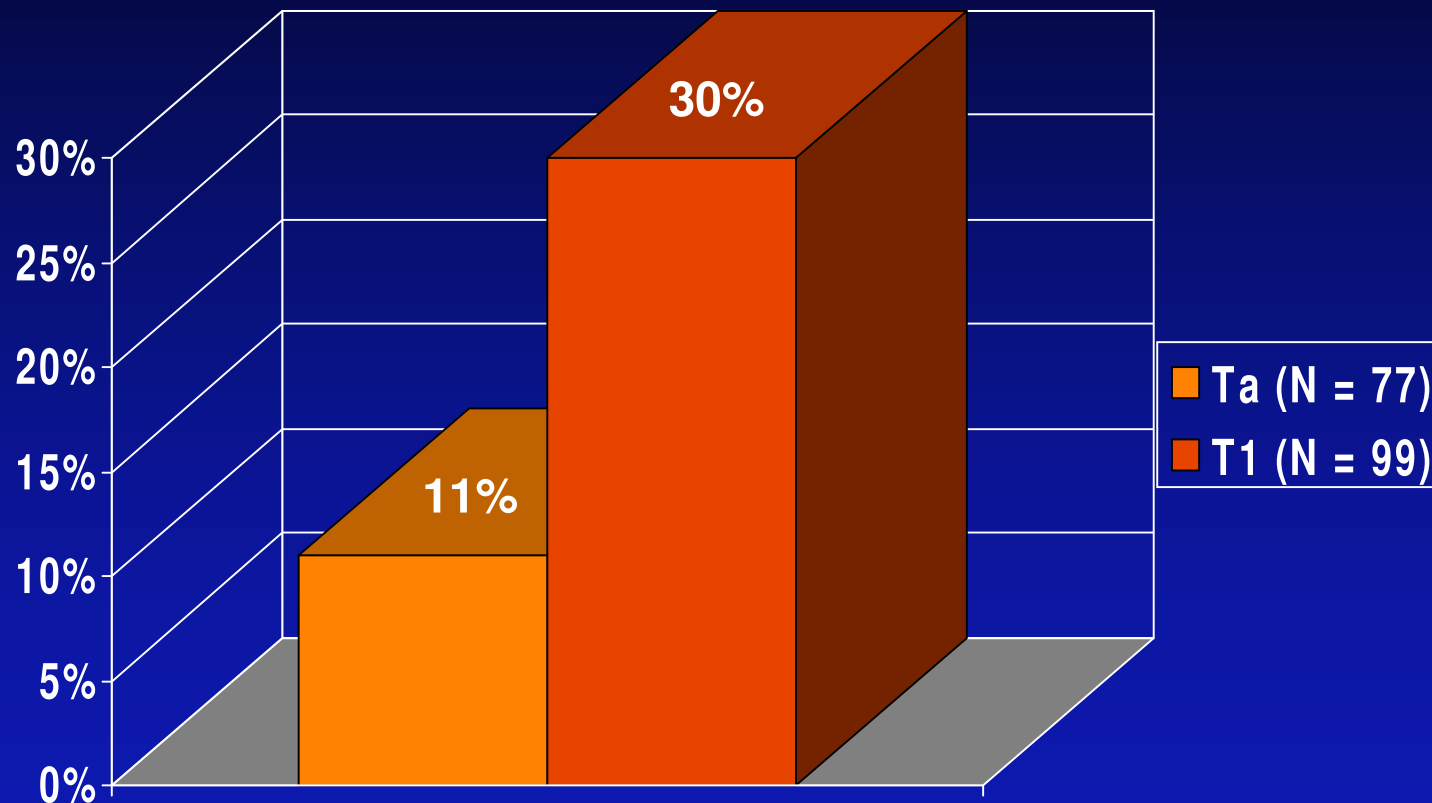
Heney et al, J Urol 130:1083, 1983

T1 Progression by Stage and Grade



Holmang J Urol 157:800, 1997

Risk of Death from Bladder Cancer by Presenting Stage



20 year follow-up, Rx with cystoscopy ± thiotepa

Holmang et al, J Urol 153:1823, 1995

Adjuvant Therapy 2005

- Cystoscopic surveillance
- Repeat TUR
- Perioperative chemotherapy
- Intravesical therapy
  - BCG
  - BCG + Interferon
  - Chemotherapy
- Cystectomy

Multiple Recurrences

- Jan 2004 -63 y/o man with multifocal Ta G2 TCC
  - Perioperative treatment with mitomycin
- April 2004 – 5 small Ta G2 TCC
  - BCG x 6 weeks
- July 2004 – 4 small Ta G2 TCC
  - BCG + interferon x 3 weeks
- Oct 2004 – 8 small, Ta G2 TCC
  - Mitomycin 40 mg/20 ml x 6
- Jan 2005 – 6 small, Ta G2 TCC
  - Doxorubicin 50 mg/50 ml x 6
- April 2005 – 4 small, Ta G2 TCC

Dr. Lamm?

Refractory G2, Ta TCC

- We desperately need more drugs!
- Cystectomy may otherwise be required
- Look for and remove carcinogens
- Diet and life style changes
- Oncovite 2 tabs BID (Mission Pharm)
- New options: immediate gemcitabine 1000mg/25cc
- Improved BCG immunotherapy

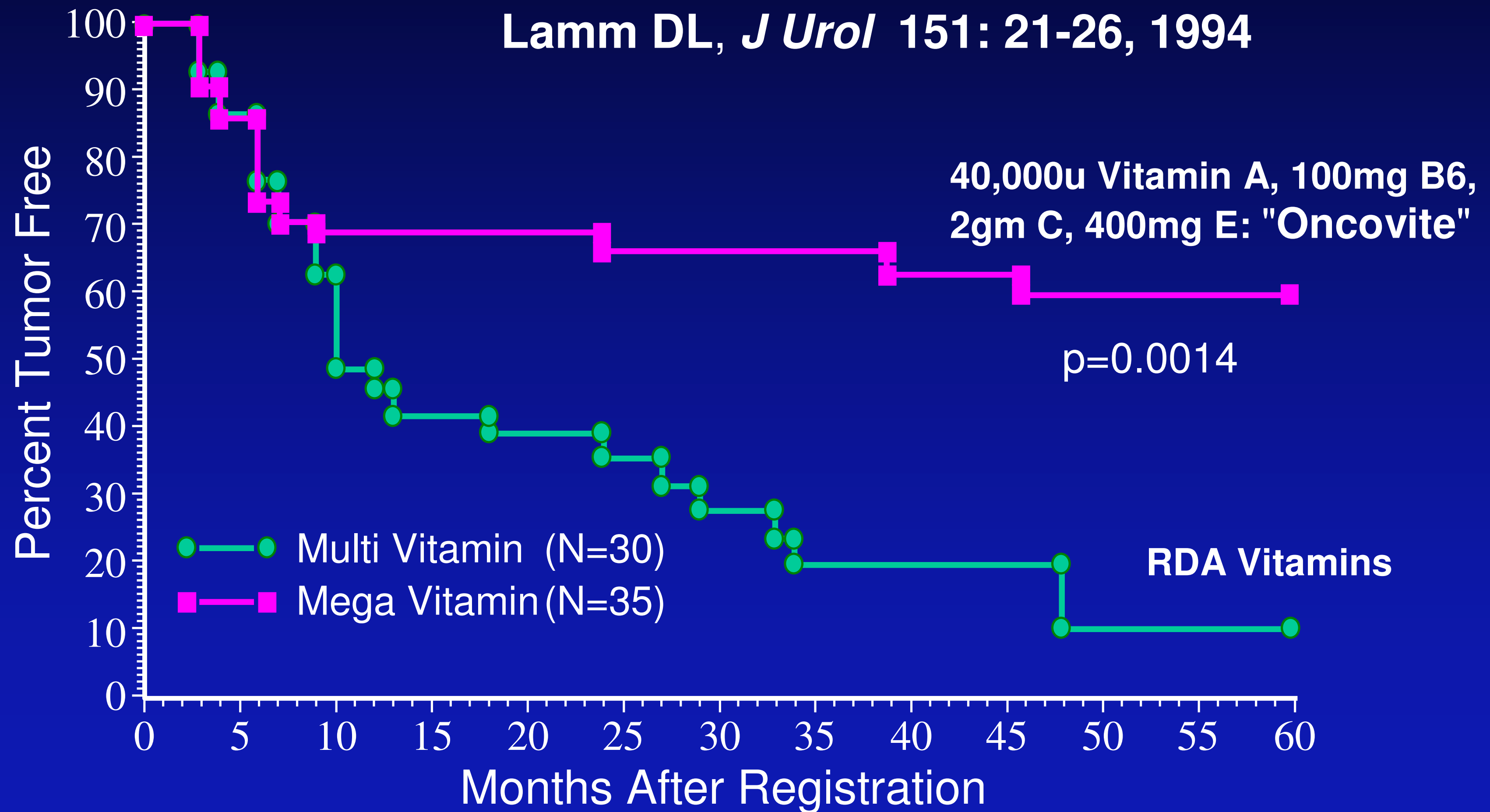
Prevention: Smoking cessation, carcinogen avoidance, nutrition

- 2-fold risk for bladder cancer associated with increased DNA adducts in smokers
  - Mutagenesis. 18:445, 2003
- Intake of fruit and vegetables in smokers decreased DNA adducts
  - Carcinogenesis. 23:861, 2002
- 286 Ta, T1 patients: Quitting ↑ recurrence-free ($P<.003$) and progression-free ($P<.001$) survival
  - J Urol 161:172, 1999

Bladder Cancer Chemoprevention

- Vitamins: A, B6, C, D, E, folic acid, C+K3
  - A: Sporn'79, Moon'83; B6: Byar'77, C: Schlegel'75, D: Konety'01; E: Michaud'00; C+K3: Gilloteaux'98; A,B6,C, E: Lamm, '94
- Allium sativum (Garlic)
  - Lau'86, Riggs'97, Lamm'01
- NSAIDS, Cox 2 inhibitors
  - Goodwin'81, Waddell'83, Earnest'92, Moon'92
- DMFO
  - Messing'88, Boone'90, Kellog'92, Loprinzi'96
- Oltipraz
  - Wattenberg & Buening'86, Moon'94, Kensler'95
- Selenium
  - Helzlsouer'89
- Soy protein, Green Tea
  - Mokhtar'88, Kemberling '03

Kaplan Meier Estimate of 5 Year Tumor Free Rate



Improved BCG Administration

- Low grade tumors respond less favorably
- Minimize tumor burden with complete resection and immediate chemotherapy
- Immune status: check the PPD; add percutaneous BCG if negative
- Weekly BCG x3 every 6 months, reducing dose 1/3, 1/10, 1/30, 1/100th

T1 TCC

- 56 y/o man with T1, G3 TCC and CIS
- BCG x 6 weeks
- Biopsy 6 weeks later demonstrates T1 G3 TCC

Dr. Theodorescu?

What are this man's chances of progressing? ...or for harboring invasive disease already?

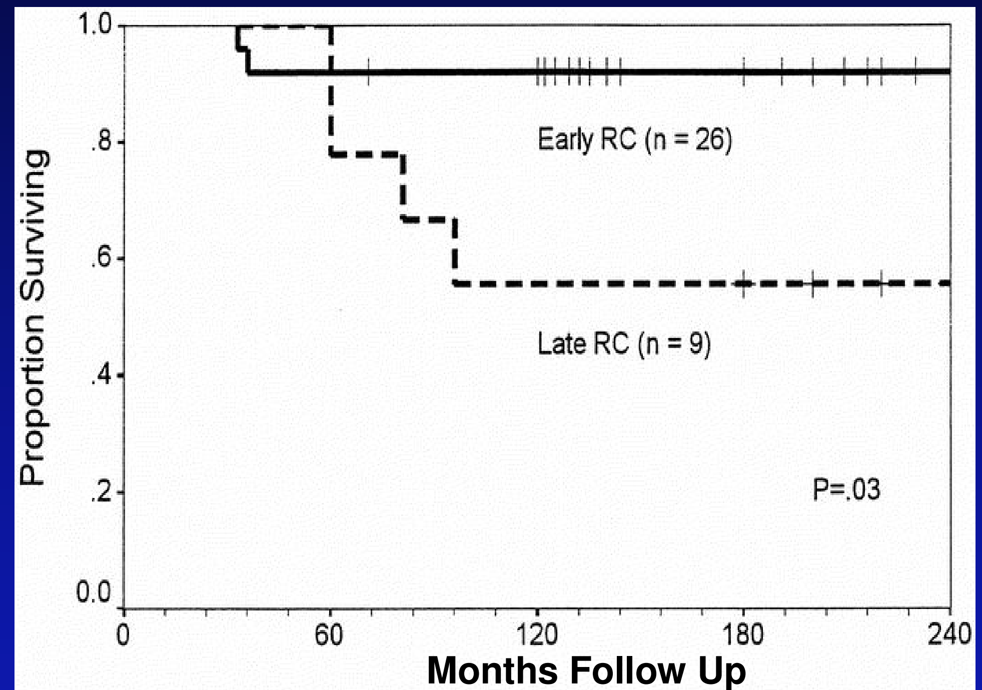
- After BCG failure each additional course of BCG carries a 7% actuarial risk of progression
  - Catalona, 1987
- In patients with T1G3 cancers, multiple tumors and/or presence of CIS are major determinants of upstaging at radical cystectomy
  - Masood, 2004
  - N=17 (single tumor, no CIS): upstaging in 1 (6%)
  - N=13 (mult. Tumor +/- CIS): upstaging in 7 (55%)

There is a Survival Advantage in patients with sTCC treated with “early” cystectomy

N=307 high risk sTCC treated with TURBT+BCG
90 underwent cystectomy for recurrent tumor: 35 superficial and 55 invasive recurrence

Of 35 with sTCC, 92% and 56% survived who underwent cystectomy <2 yrs after initial BCG therapy vs. >2 yrs

Multivariate analysis: ↑ survival in patients who underwent earlier cystectomy for sTCC relapse



Herr, 2001

Defining BCG refractory sTCC

- 93 patients received a 6-week induction course of BCG
- Evaluated for response after 3 and 6 months
- 57% were negative for tumor at 3 months
- 80% of the patients were tumor-free at 6 mo
- Tumor-free interval during 24 mo followup best predicted by response to BCG at 6 mo

Herr, 2003

Excellent Prognosis of sTCC with cystectomy for sTCC

- 5 and 10 year cancer-specific survival rates as a function of pathological tumor stage:
- Amling 1994
  - pT0 (43) 80% and 66%
  - pTa (11) 88% and 75%
  - pTis (19) 100% and 92%
  - pT1 (91) 76% and 62%
- Stein 2001
  - pT0, pTa, pTis (N0): (208) 89% and 85%
  - pT1 (N0): (194) 83% and 78 %

Practical approach to T1G3 after 1st BCG failure

Initial Treatment

T1G3

BCG

1st Evaluation

Multiple tumors or CIS (original or rec)

Yes

No

Cystectomy

Second Line Intravesical Tx

2nd Evaluation (>6 mo)

Cystectomy

Positive Cytology

- 71 y/o man with T1 G3 TCC with CIS
- BCG x 6 weeks
- After last dose had severe irritative sx and fever to 102 x 24 hours
- 6 weeks later – cysto negative and cytology positive

Dr. Ratliff?

Issues Highlighted by Case

- What defines BCG intolerance & contra-indication for further BCG therapy
- Approach to patients with positive cytology post-BCG

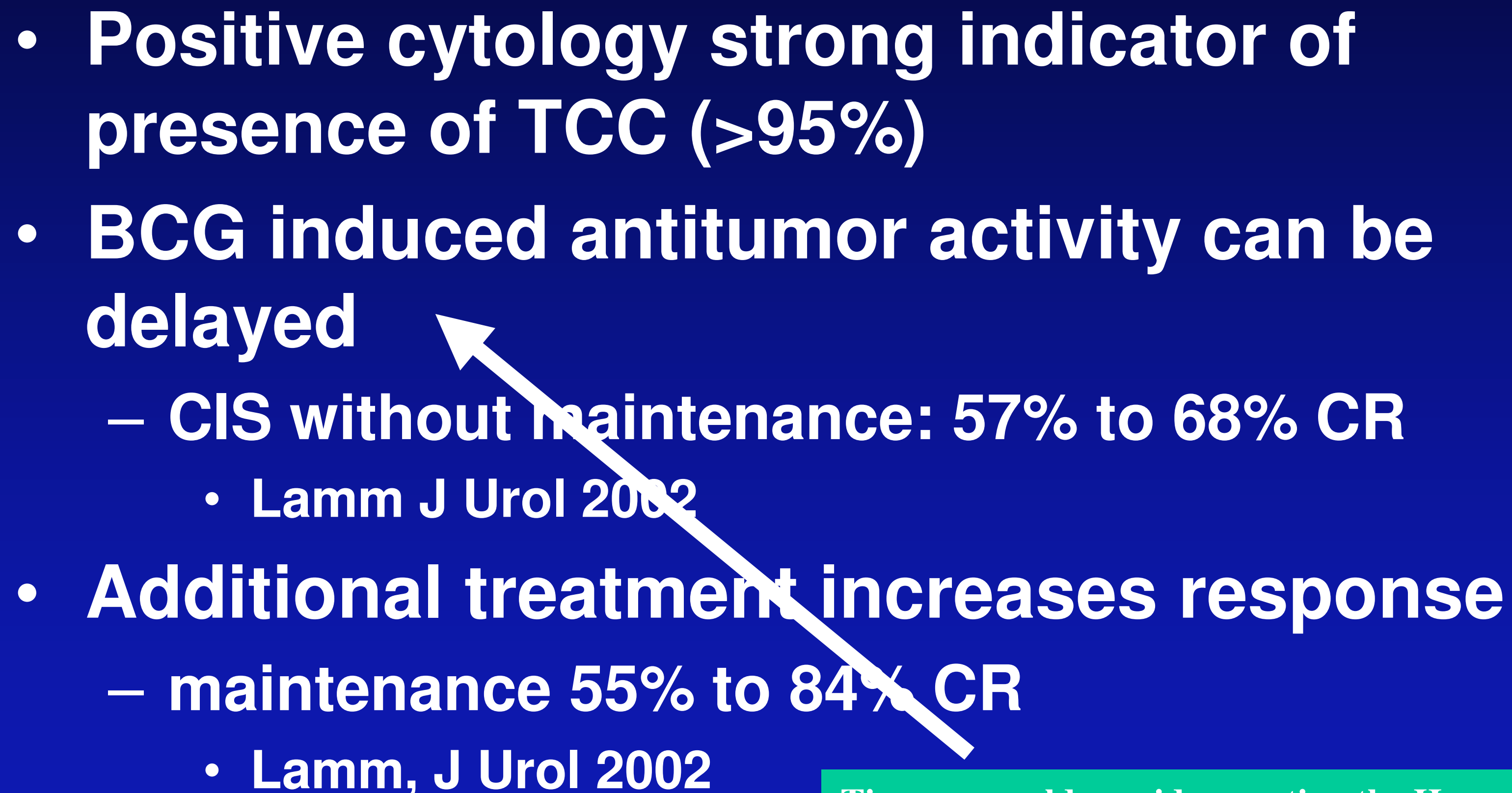
Issue 1: Fever & Irritative Symptoms after BCG

- Irritative symptoms occur in 35-90% of patients (median, 75%)
  - AUA Bladder Cancer Guidelines
- Transient fever > 102 in 1-2% at each instillation
  - Lamm, DL and Torti, FM, Cancer Journal for Clinicians, 1996
- Fever longer than 24 hrs considered infection and treated accordingly

Issue 1: Fever & Irritative Symptoms after BCG

- Reduction of transient symptoms (30-50%) by either:
  - BCG dose reduction (1/2 to 1/3)
    - Martinez-Pineiro, BJU International 2002
  - Slow dosing BCG on an every other week schedule
    - Bassi, Eur. Urol. 2002
- Current patient not considered BCG intolerant

Issue 2: Positive Cytology Post-BCG



- Positive cytology strong indicator of presence of TCC (>95%)
- BCG induced antitumor activity can be delayed
  - CIS without maintenance: 57% to 68% CR
    - Lamm J Urol 2002
- Additional treatment increases response
  - maintenance 55% to 84% CR
    - Lamm, J Urol 2002

Tim, you could consider quoting the Herr paper from my section to tie these 2 sections together

Issue 2: Positive Cytology Post-BCG

- Determine source of positive cytology
  - >80% in bladder while • 20% outside bladder (ureter, kidney, prostatic ducts)
- At U. Iowa routinely restage patients with post-treatment positive cytology
  - Bladder barbotage, random bladder bx, prostatic urethra bx, upper tract washings, bilateral retrograde pyelograms

Treatment

- If disease localized to bladder, 3 reduced doses BCG (1/3, 1/10, 1/10) with IFNά (50 MU followed 1 mo later with another 3 treatment cycle
- Evaluate at 6 mo.

Positive Cytology

- 53 y/o non-smoker
- History of Ta, G2 TCC 2 years ago
- Positive cytology
- IVP negative
- Bladder and prostatic urethral biopsies negative
- 3 months later – positive cytology

Dr. Lamm?

Positive Cytology, Negative Bx

- 0.2% Methylene blue vital staining will increase yield of biopsy
- UroVysion should be positive, but can be checked if there are doubts
- Differential wash: bladder and each ureter for cytology
- Ureteroscopy with biopsy of any suspicious urothelium

Unusual Histology

- 58 y/o man with T1 micropapillary bladder cancer

Dr. Theodorescu?

Clinical demographics of "Micropapillary" bladder cancer

Literature review 1966 to 3/2005

N	Country	% of All BC	Mean Age	M:F	Author	Year
18	USA	n/a	67	5:1	Amin	1994
20	Sweden	0.7%	69	2:1	Johansson	1999
20	Australia	n/a	69	4:1	Samaratunga	2004
38	Mexico	6%	68	37:1	Alvarado	2005
7	Several	n/a	60-70	n/a	Case reports	1995-2001

Search Terms: "micropapillary bladder cancer (carcinoma)"

What is micropapillary (MPC) bladder cancer?

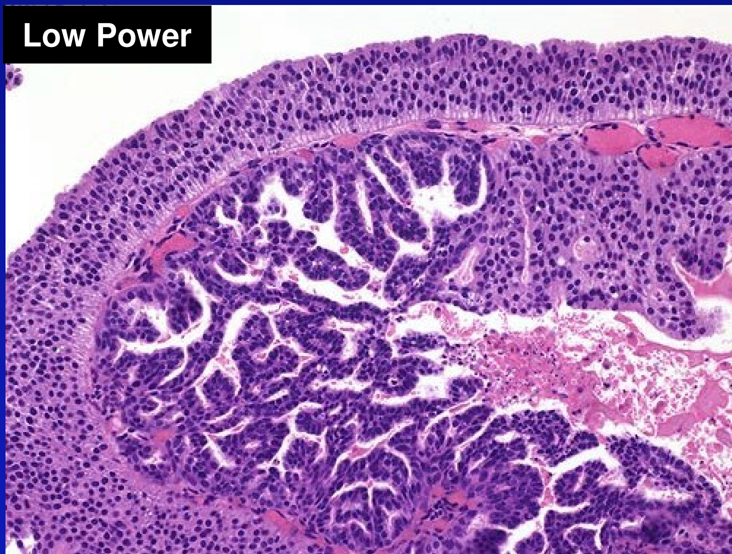
Clinical Features

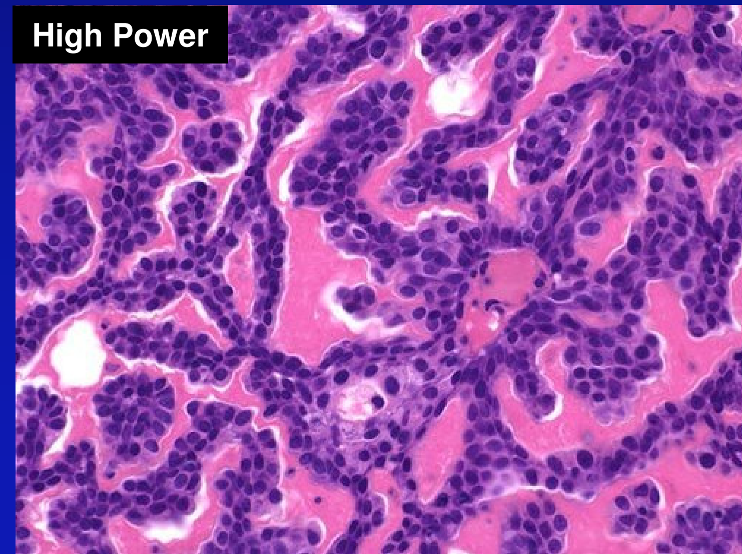
- Variant of carcinoma in various anatomic sites (breast, urinary bladder, lung, and salivary glands)
- High propensity for lymphovascular invasion and lymph node metastases
- Often high-stage disease at presentation
- Tumors with <10% MPC have a high chance of detection at an early stage
- Poor clinical outcome compared with that of patients with urothelial carcinoma (N=38, 40% DFS at 3yrs)
- Radiation and chemotherapy do not seem to be effective

What is micropapillary (MPC) bladder cancer?

Pathology

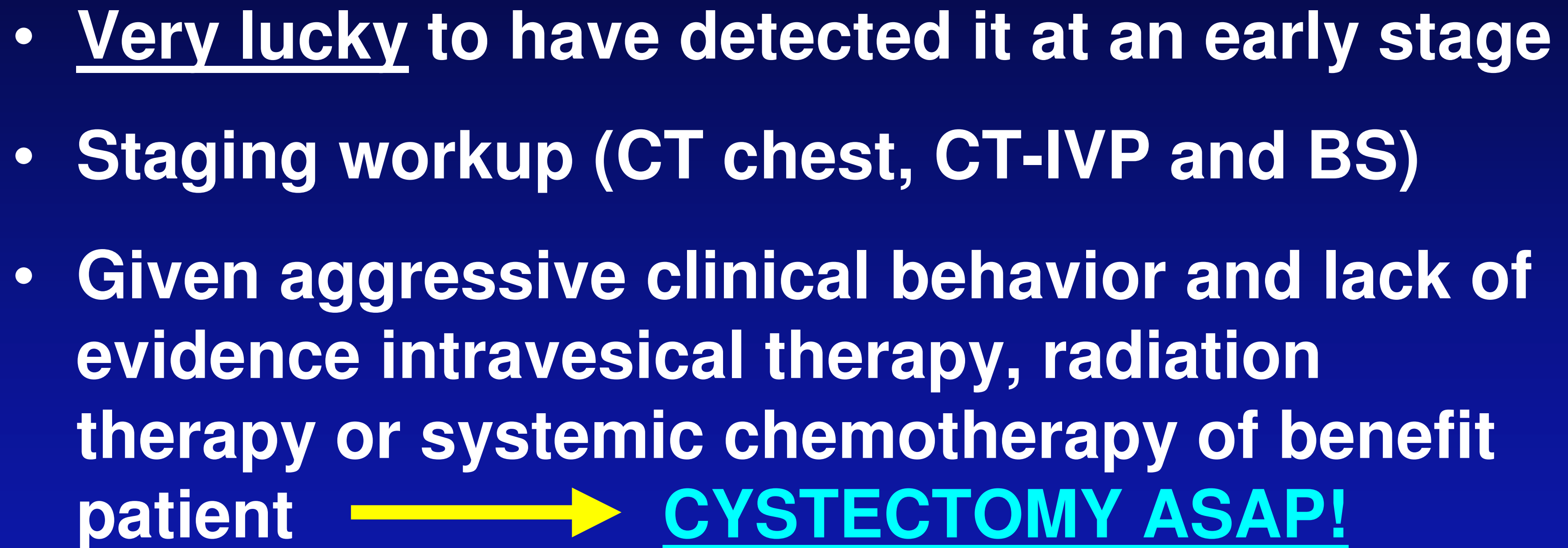
- immunohistochemical staining pattern supports that MPC is a variant of adenocarcinoma
- small tight clusters of neoplastic cells floating in clear spaces resembling lymphatic channels
- pattern is mixed with a variable component of conventional urothelial carcinoma or other variants





Figures from: webpathology.com

58 y/o man with T1 MPC



Carcinoma in Situ

- 68 y/o woman former smoker with CIS
- BCG x 6 weeks
- Biopsy 6 weeks later demonstrates CIS

Dr. Ratliff?

Issues Highlighted by Case

- Conservative vs radical therapy
- Conservative treatment options

Issue 1
Conservative vs Radical Therapy

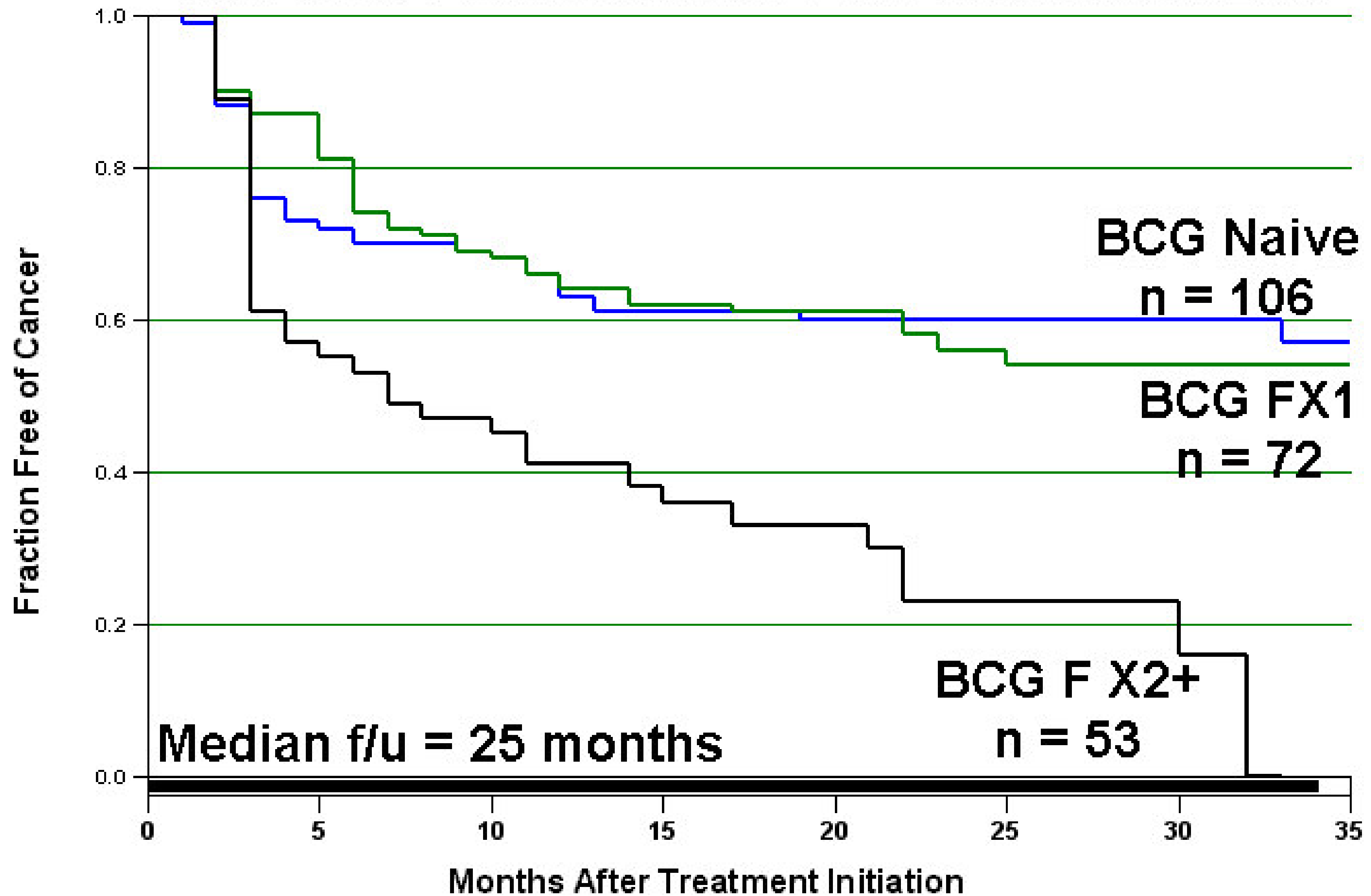
- **Natural history CIS progression ≅ 7% annually and 3.3% at 6 mo**
  - **Cheng, *Cancer*, 1999**
  - **Millan-Rodriquez, *J Urol*, 2000**
- **Cystectomy mortality ≅ 2%**
- **Thus another 3 mo for additional conservative therapy is acceptable risk**

Issue 2: Treatment Options

- BCG induced antitumor activity can be delayed
  - ¬CIS without maintenance: 57% to 68% CR
    - ¬Lamm *J Urol* 2002
- Additional treatment increases response
  - ¬ maintenance 55% to 84% CR
    - ¬Lamm, *J Urol* 2002

Issue 2: Treatment Options

- Chemotherapy for BCG failures provides poor response rates
  - ≅ 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)



Maymi et al, AUA Abstract 918

Treatment

- Low dose BCG + IFN (50 MU)
- Evaluate at 3 and 6 mo.
- If fail at 6 mo., cystectomy

Recurrent High Grade TCC

- 65 y/o woman with a history of Ta G2-3 TCC
- Intravesical BCG for 6 weeks
- Regular surveillance cystoscopy
- 2 years after her initial tumor has a 2 cm, Ta G3 TCC

Dr. Lamm?

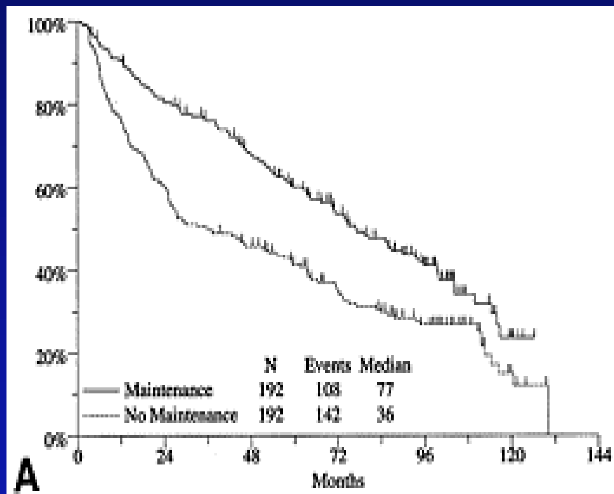
High Grade Recurrence after BCG Induction

- Meta analysis shows BCG reduces progression, but only with maintenance
- Repeated 6 week treatments is historically suboptimal, suppresses cytokines, risks immunosuppression, and is ineffective in a controlled trial
- 3 weekly BCG (extending if there are no symptoms), repeating at 3 months, then q. 6 months would be my choice for her

3 Week Maintenance BCG

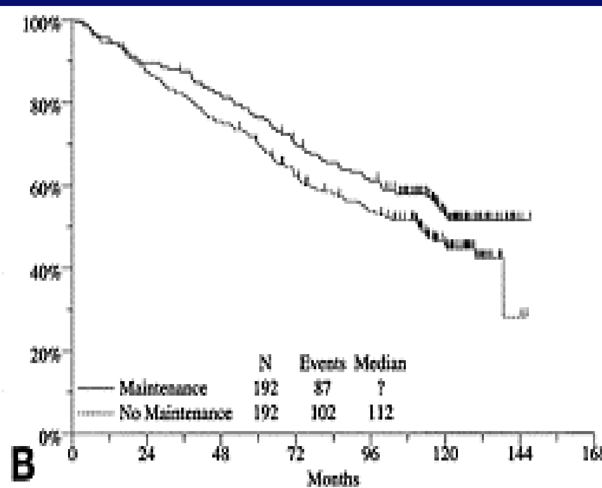
550 pts. 6 wk vs. 3 wk maintenance at 3, 6, 12, 18, 24, 30, & 36 months

Recurrence -free Survival



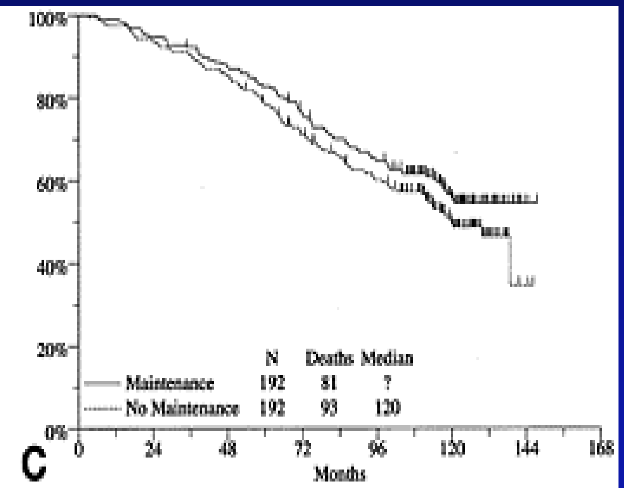
p < 0.0001

Worsening -free Survival



p = 0.04

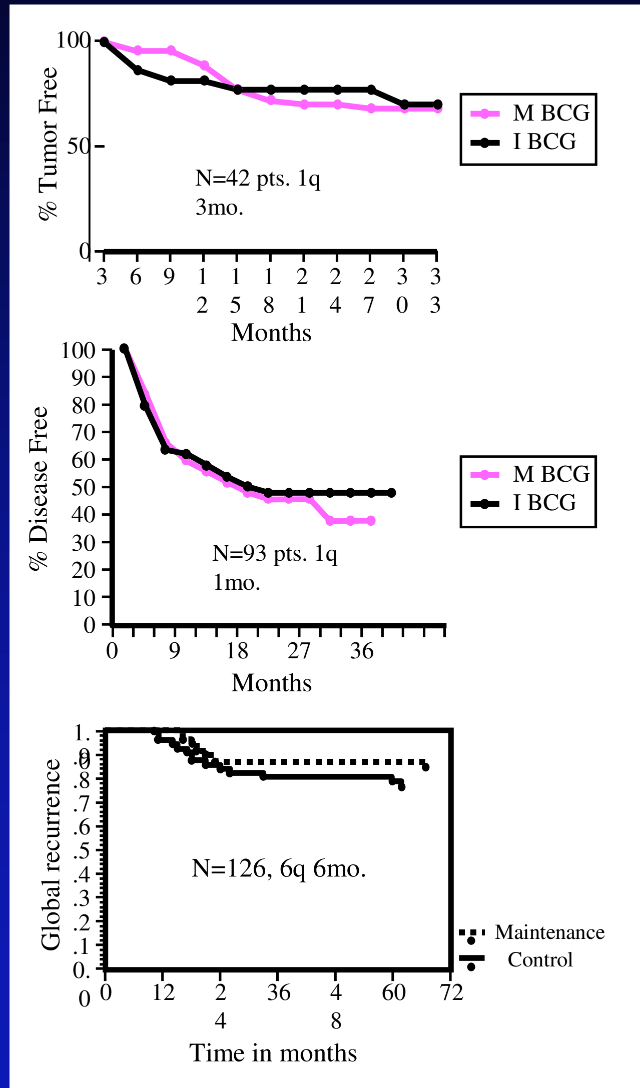
Survival

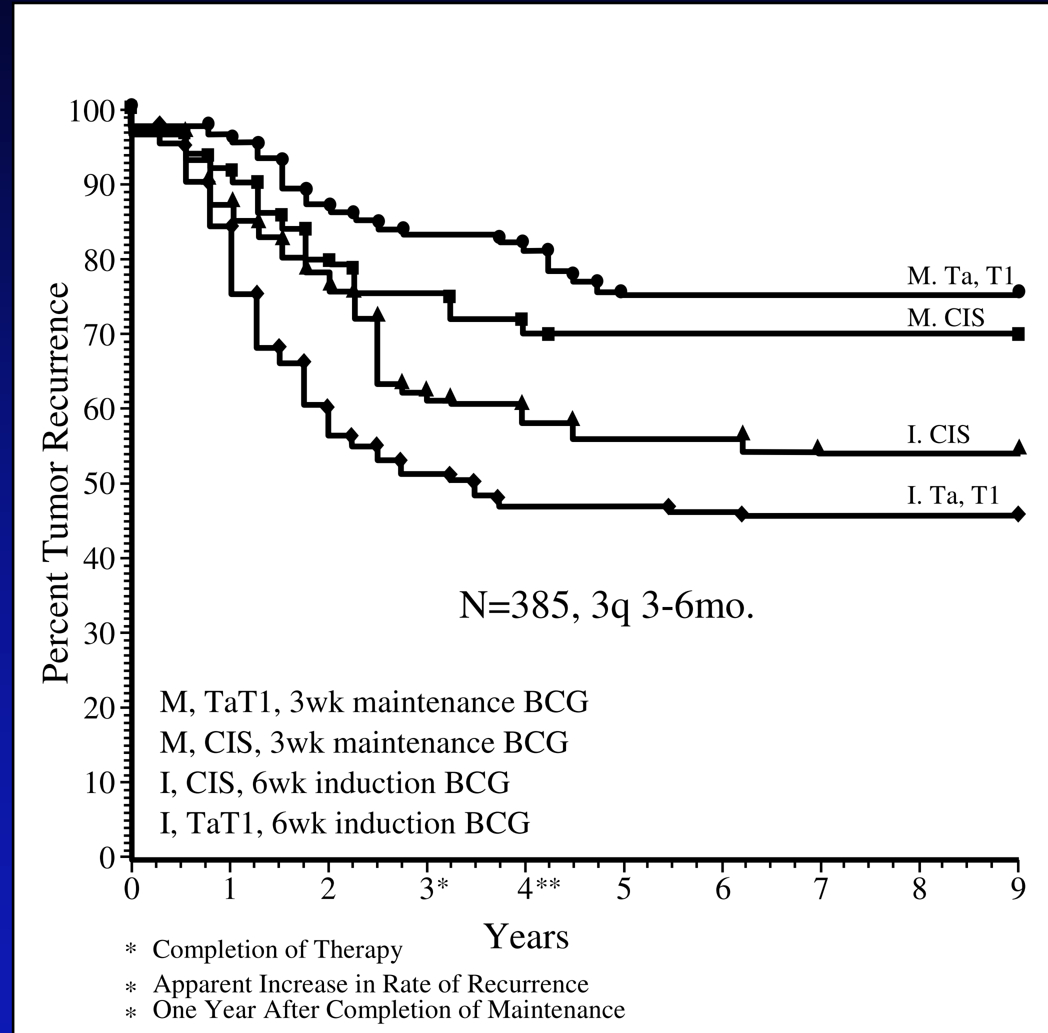


p = 0.08

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

BCG Maintenance: Not Created Equal





Meta Analysis: BCG vs Control

24 trials with 4863 patients were eligible:

Start of Patient Entry:	1978 to 1993
Date of Publication:	1982 to 2001
Duration of Follow Up:	Median: 2.5 years Maximum: 15 years
Five BCG strains:	TICE, Connaught, Pasteur, RIVM, A. Frappier

Sylvester, R: J Urol, 2002

Progression: Maintenance BCG

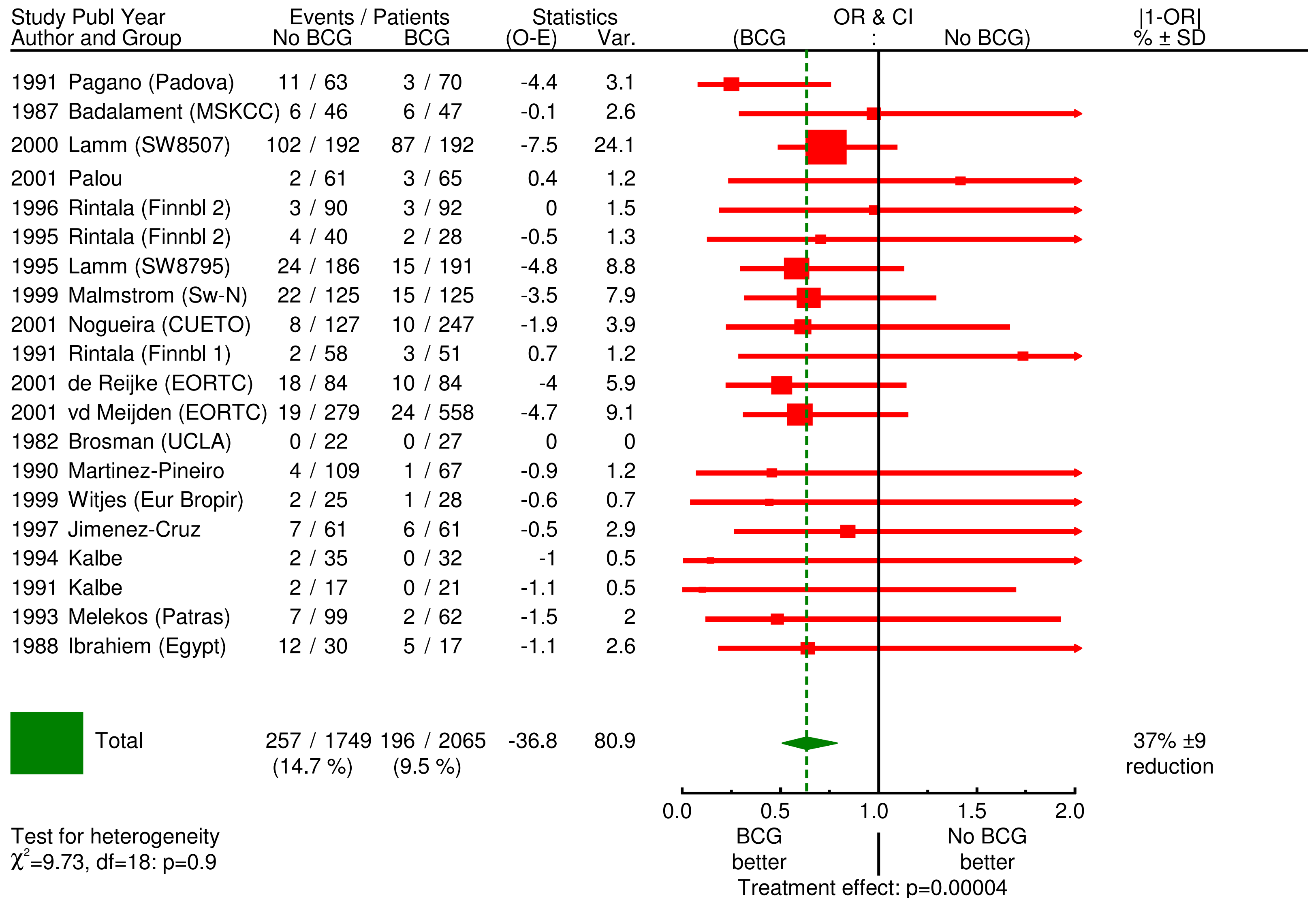
	Patients	No BCG	BCG	OR
No Maint	1049	10.3%	10.8%	1.28
Maintenance	3814	14.7%	9.5%	0.63

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.

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

- Use perioperative therapy for low-risk TCC
- Use maintenance BCG for high-risk TCC
- Lower the dose for BCG toxicity
- Don’t abandon BCG therapy for CIS at 3 months
- Recurrent T1 disease is dangerous
- Be more aggressive with micropapillary & small cell histology
- Don’t follow your patient to the grave – consider cystectomy when local Rx fails