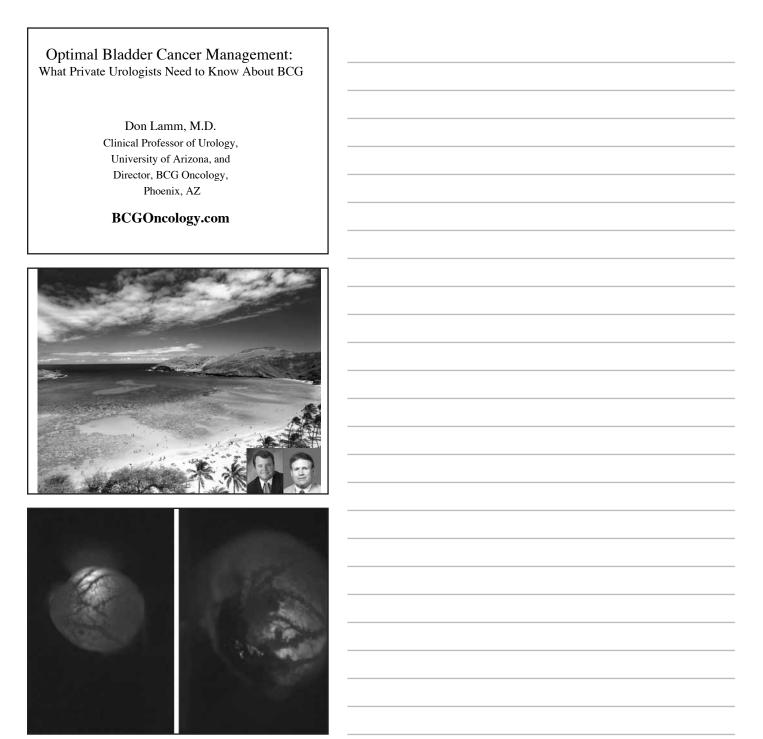
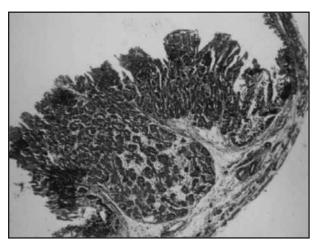
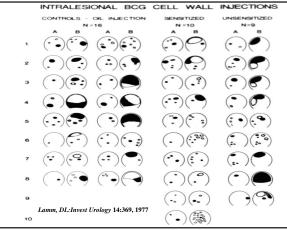
### 18th Annual PERSPECTIVES IN UROLOGY POINT COUNTERPOINT 2009

# What the Community Urologist Needs to Know About BCG

~ Donald L. Lamm, MD



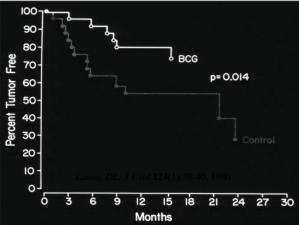




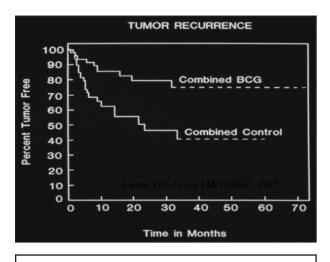


## BCG in Bladder Cancer

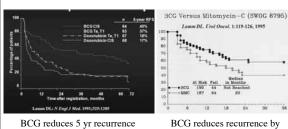
- 1976: Morales- 12 fold reduction in recurrence in 9 bladder cancer patients
- 1977: Lamm reports success in controlled animal studies of bladder cancer
- 1980: Lamm reports successful randomized clinical trial
- 80's-90's: Multiple comparison studies show BCG to be superior to chemotherapy







## BCG vs Chemotherapy



BCG reduces 5 yr recurrence by 19-28% vs Adriamycin

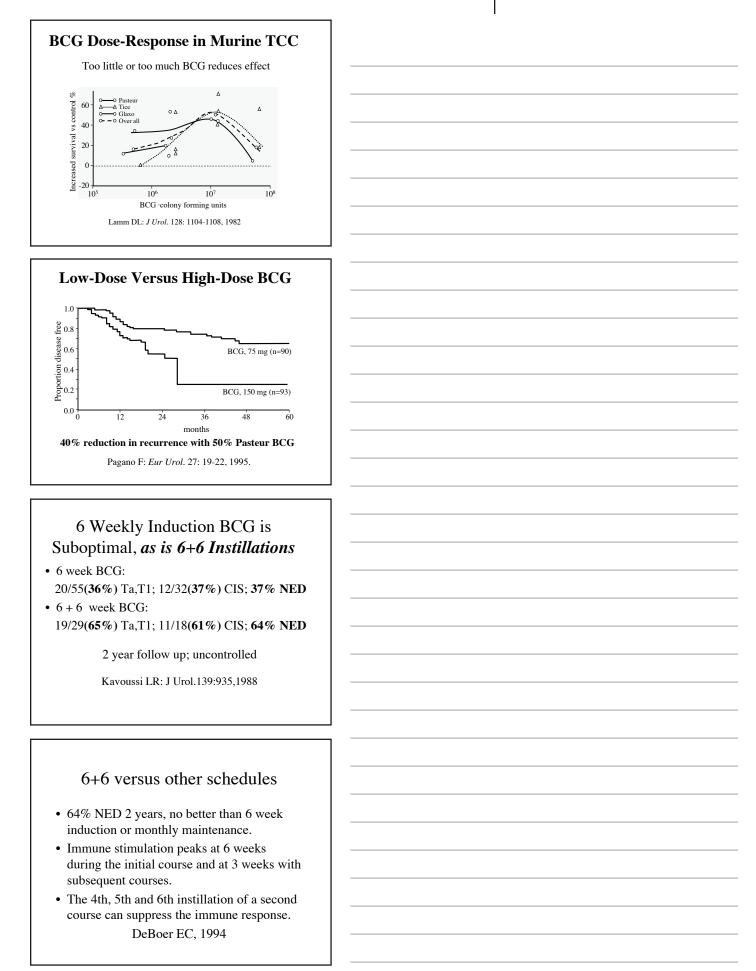
## **BCG** Present

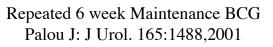
11% vs Mitomycin C

- BCG efficacy established as superior to chemotherapy
- Risk versus benefit and optimal schedule- questions remain
- Benefit in reducing progression and mortality questioned

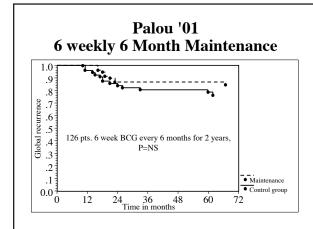
## What is the best BCG regimen?

- Weekly x 6?
- Repeat weekly x 6 for recurrence?
- Maintenance BCG?
- Dose?



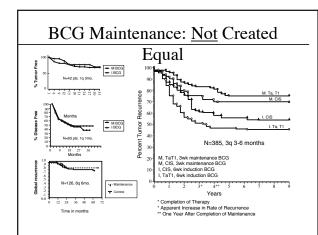


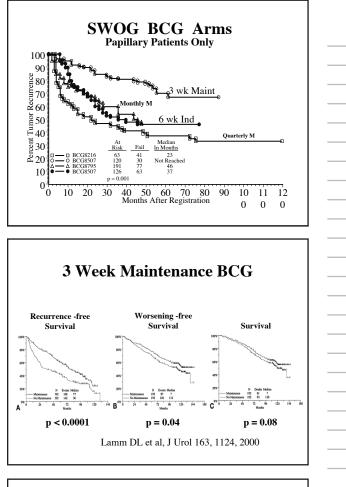
- 126 pts randomized to 6 wk induction v. 6 wk maintenance every 6 months for 2 years
- Mean follow-up 79 months
- 16/61 (26%) recurrence in induction v. 10/65 (15%) with repeated 6 wk BCG
- 11/65 (34%) completed maintenance
- No significant advantage observed



#### Second Induction Course of BCG

Author	Ν	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 pl	us interf	eron: 53	3% recurren	ce free 26 m.





#### 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

Treatment	Progression
No BCG	304/2205 (13.8%)
• BCG	260/2658 ( 9.8%)
Difference	4.0%
Odds ratio (OR)	0.73
Odds reduction	27% (95% CI: 11%-40%)
P Value	0.001

Progression:
Disease Type

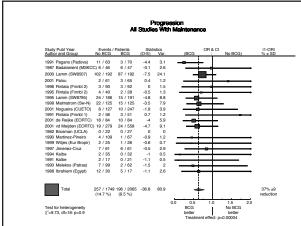
Pa	tients	No BCG	BCG	Total	OR
Pap	2880	8.1%	5.1%	6.4%	0.68
CIS	403	16.2%	11.8%	13.9%	0.65

Although their prognosis is different, the size of the treatment effect was similar in papillary tumors and CIS

## Progression: Maintenance BCG

Patients	N	lo BCG	BCG	OR
No Maint	1049	10.3%	10.8%	1.28
Maintenance	3814	14.7%	9.5%	0.63
Test for he	eteroge	neity: P =	= 0.008	

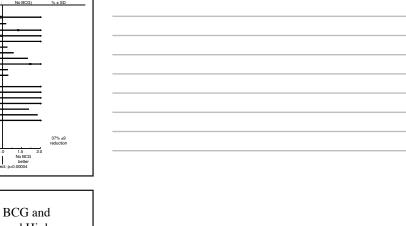
BCG was only effective in trials with maintenance, where it reduced the risk of progression by 37%, p = 0.00004.

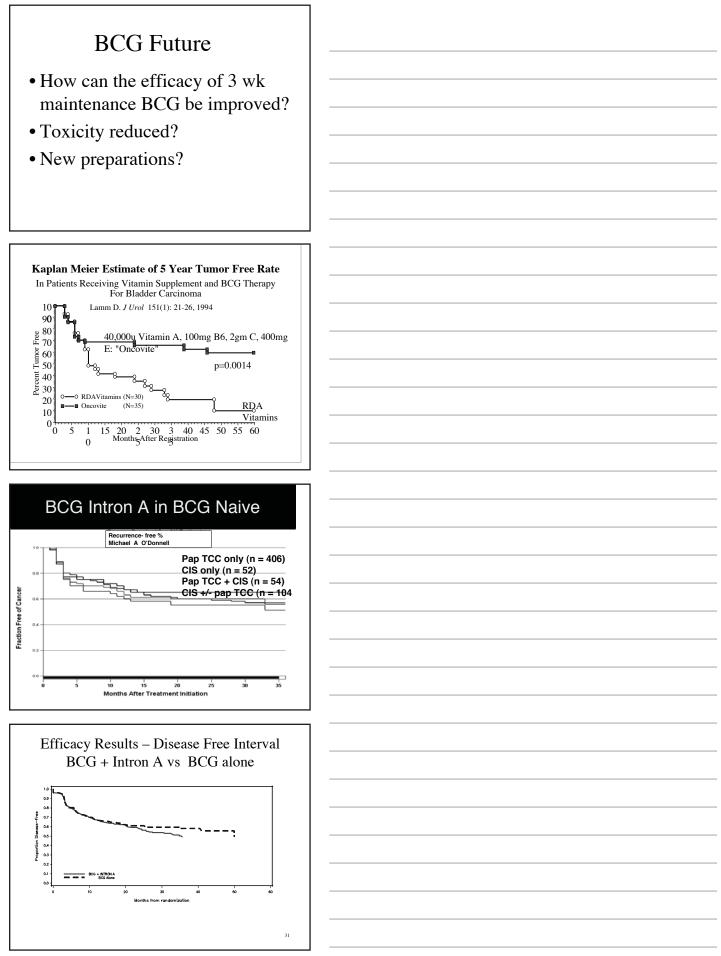


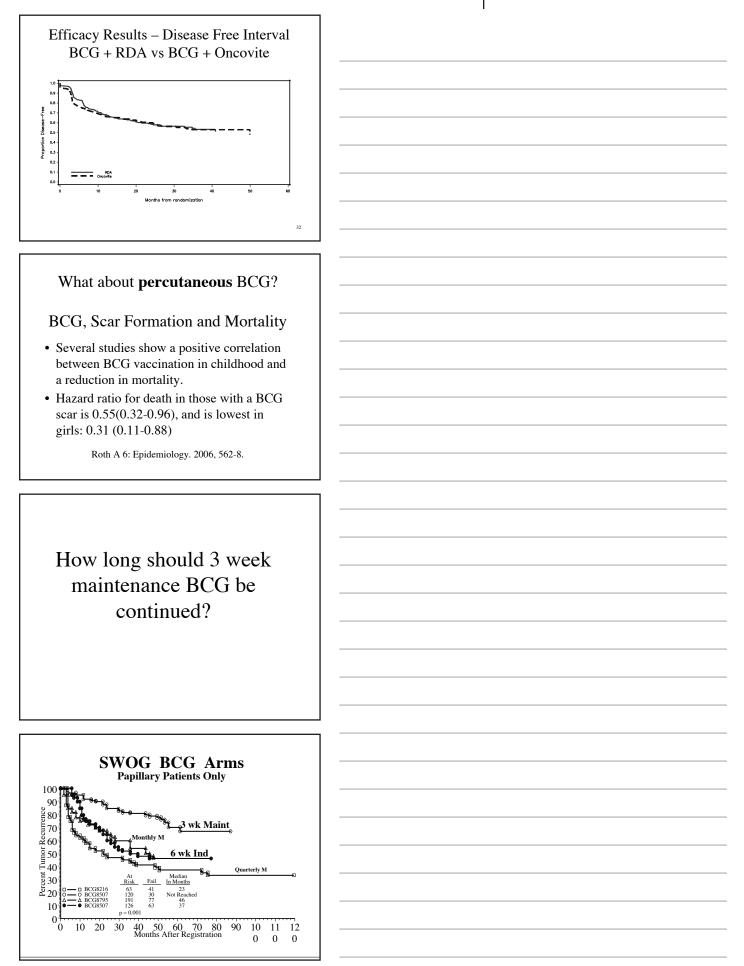
Long-Term Efficacy of Epirubicin, BCG and BCG plus Isoniazid in Intermediate and High Risk Ta,T1 Bladder Cancer

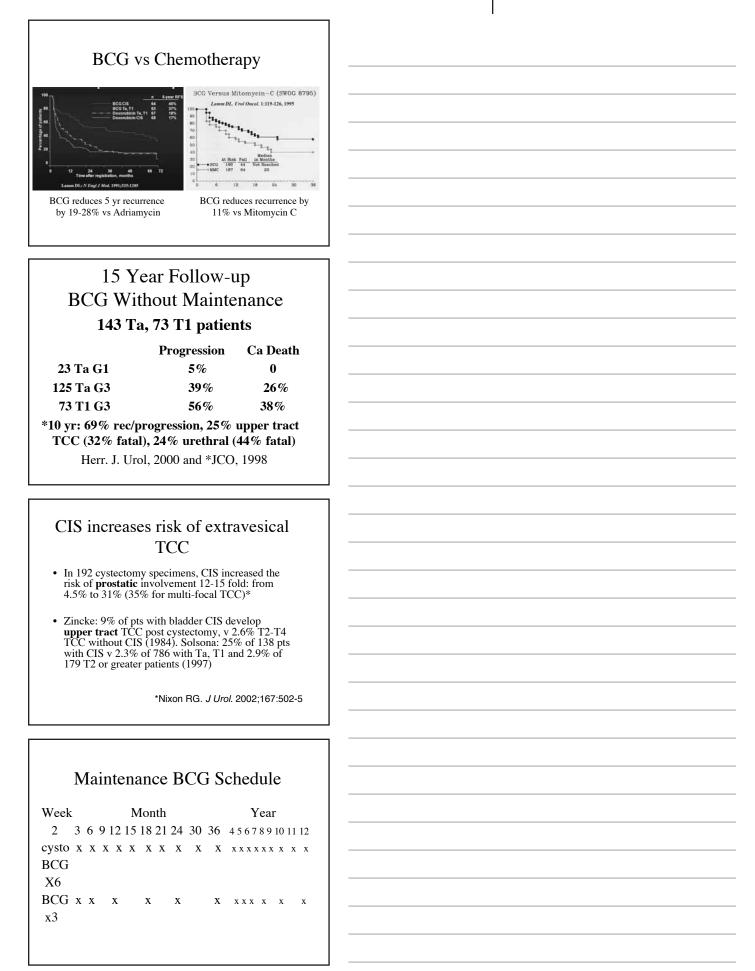
- 957 pts randomized to 6 wk Epirubicin vs 3 wk Maintenance BCG.
- CIS excluded. 9.2 yr follow up.
- Time to recurrence (.0001), time to distant metastasis (.03), overall (.02) and disease specific survival (.03) **all** significantly favor BCG
- Advantage consistently *greater* in intermediate than high risk patients

Sylvester RJ: EAU Abstract 907, 2008









#### Maintenance BCG Reduces the Death in Cystectomy Patients

- 501 evaluable pts randomized to induction vs 3 wk BCG at 3,6,12,18,24,30, and 36 months
- Niether stage (T2 vs Tis/T1, P=0.18, NS) nor delay in cystectomy reduced survival
- 3wk BCG *significantly* reduced mortality in failure/cystectomy pts: HR 0.37, p=0.017

#### 3 Week Maintenance BCG Reduces Death in Cystectomy Pts

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Lerner S: J Urol. (2007), 177: 1727

#### Maintenance BCG Reduces the Incidence of Prostate Cancer Lamm. J Urol 161:285, 1999

- 385 bladder cancer pts randomized to 6wk induction vs induction + 3 wk maintenance
- With 8+ yr follow up, second primary Ca developed in 23% of induction & only 13% of those on maintenance BCG (P<0.014)
- Prostate Cancer reduced from 14 (6.9%; 3 C, 3 D) to 5 (3.3%; 1C, P=0.04)

### Conclusions

- Current preparations are not significantly different in efficacy, and attempts to breed "superior BCG" have been unsuccessful.
- Molecular engineering, however, with insertion of human cytokine genes such as IL-2 or interferon gamma are very promising

### Conclusions

- BCG has had a controversial past, but is currently the treatment of choice for aggressive superficial bladder cancer
- Controlled trials clearly demonstrate superiority over current intravesical chemotherapy

### Conclusions

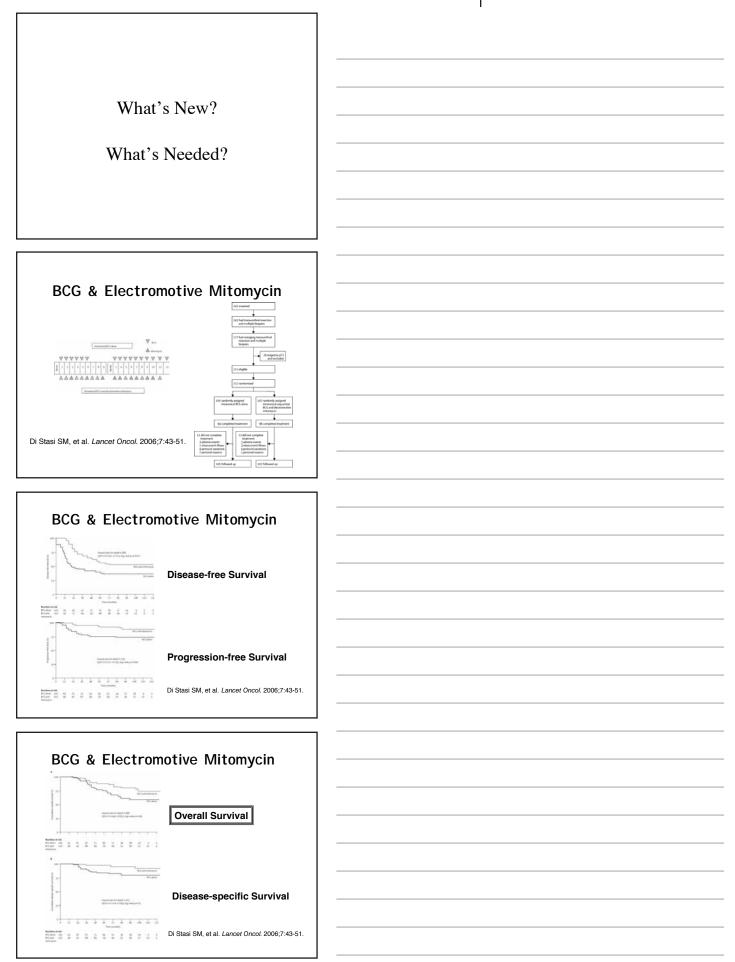
- 6 week induction BCG is suboptimal; more BCG is better.
- Maintenance with single instillations monthly or quarterly is suboptimal.
- Repeated 6 week instillations is suboptimal and potentially immunosuppressive.
- Too much BCG reduces response and increases toxicity.

#### Conclusions

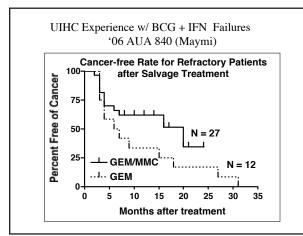
- The risk of progression in patients with CIS, high grade, and T1 TCC is long term- longer than the protection afforded by induction BCG.
- Meta-analysis of 24 controlled studies including 4,863 patients confirms that BCG significantly reduces progression, but *only* if maintenance is used.
- Maintenance BCG reduces progression by 37%, p = 0.00004.

### Conclusions

- High dose vitamins A, B6, C and E appear to further reduce recurrence in BCG treated patients
- Combination BCG plus interferon alfa may be superior to BCG alone, and rescues 60% of BCG failures
- Recombinant BCG may be superior
- BCG should be evaluated in other malignancies



Gemcitabine	
<ul> <li>N = 30</li> <li>BCG Refractory or Intolerant</li> <li>2 courses 2 g/100 mL twice weekly for 3 weeks separated by 1 week of rest</li> <li>Dalbagni G, et al. J Clin Oncol. 2006;24:2729-2734.</li> </ul>	
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.	
Multi-Agent Intravesical Chemotherapy	
• Multidrug regimens: nearly always better in advanced TCC	
• Combine to increase cell kill without increased toxicity	
<ul> <li>Most frequent DLT for intravesical chemotherapy is cystitis</li> </ul>	
• Combine drugs with differing mechanisms of action, one or more without vesicant (irritative) side effects Mike O'Donnell, 2006	
Vesicant Profile of Chemotherapeutic Agents	
Vesicants       Non-Vesicants         Platinums√       Gemcitabine*         Alkylating agents       5-FU*         Mitomycin ✓       5-FU*         Anthracyclines       Cytarabine *         Adriamycin ✓       Methotrexate*         Epirubicin ✓       Pemetrexed (Alimta)         Valrubicin ✓       Bleomycin*         Taxanes       Thiotepa * ✓         Paclitaxel (vesicant)       Docetaxel (irritant) *→	



#### Other Active Combinations

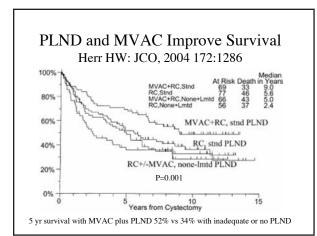
Variations of Adriamycin, Mitomycin, Gemcitabine, and Docetaxel chemotherapy

- Sequential Adriamycin-Gemcitabine X 6
- Sequential Gemcitabine-Docetaxel X 6
- Sequential Generatione-Docetaxel X 6
   Sequential Docetaxel-Mitomycin X 6
- Sequential Docetaxel-Mitolifychi X 6
   Sequential Adriamycin-Docetaxel X 6
- Sequential Adriantychi-Doceta
- Double sequential Adriamycin-Gemcitabine X3 followed by Docetaxel-Mitomycin X3

Mike O Donnell, 2006, MD Anderson Bladder Cancer Meeting

#### 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.



#### What the Community Urologist Needs to Know About BCG

