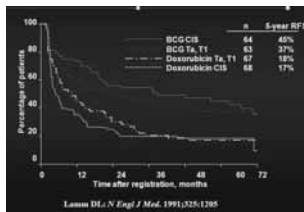
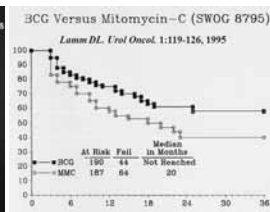


BCG vs Chemotherapy



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



BCG reduces recurrence by 11% vs Mitomycin C

BCG Present

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

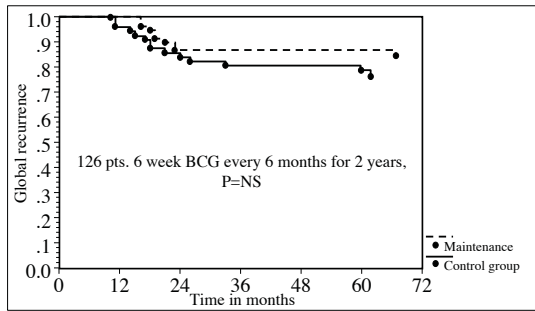
What is the best BCG regimen?

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

Repeated 6 week Maintenance BCG
 Palou J: J Urol. 165:1488,2001

- 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

Palou '01
6 weekly 6 Month Maintenance

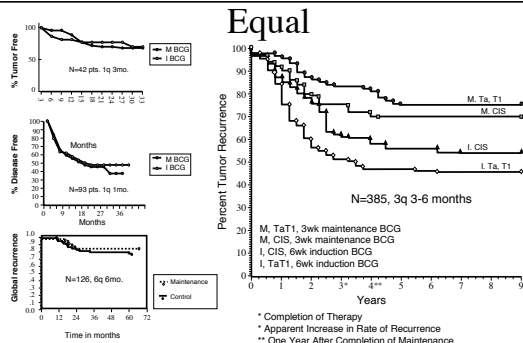


Second Induction Course of BCG

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.

BCG Maintenance: Not Created



Progression:
Disease Type

	Patients	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

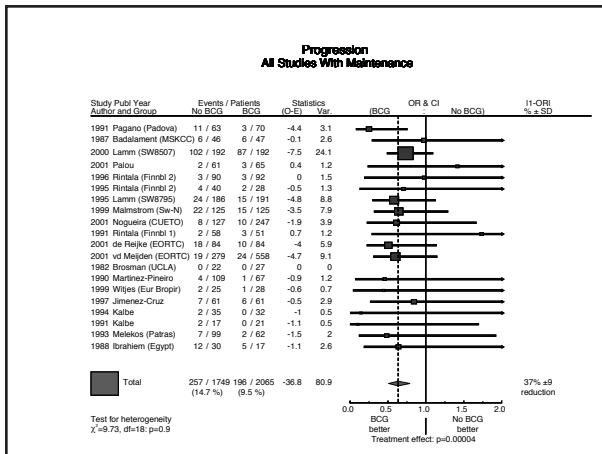
Although their prognosis is different, the size of the treatment effect was similar in papillary tumors and CIS

Progression:
Maintenance BCG

	Patients	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.



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

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

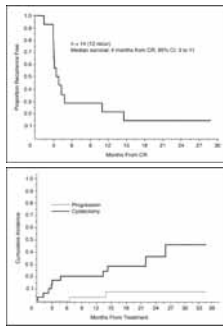
- The risk of progression in patients with CIS, high grade, and T1 TCC is long term- longer than the protection afforded by induction BCG.
- Meta-analysis of 24 controlled studies including 4,863 patients confirms that BCG significantly reduces progression, but *only* if maintenance is used.
- Maintenance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

- 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.

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
- 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

Vesicant Profile of Chemotherapeutic Agents

Vesicants	Non-Vesicants
Platinums ✓	Gemcitabine*
Alkylating agents	5-FU*
Mitomycin ✓	Cytarabine *
Anthracyclines	Methotrexate*
Adriamycin ✓	Pemetrexed (Alimta)
Epirubicin ✓	Bleomycin*
Valrubicin ✓	Thiotepa * ✓
Vinca Alkaloids	
Taxanes	
Paclitaxel (vesicant)	
Docetaxel (irritant) *→	

✓ moderate-severe cystitis reported * mild cystitis reported

