FDA/AUA Panel NMIBC

Are the current data that we have regarding BCG efficacy of good enough quality to establish a non-inferiority margin for trials today?

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Risk Stratification - EAU

- Low - TaG1 solitary, primary, < 3cm - 50% patients
- Intermediate - Multifocal, recurrent TaT1, G1-2, 35% patients
- High - CIS, any G3(Ta or T1) and multiple and recurrent and large (> 3 cm) Ta G1G2 tumors

  - 15% of patients

EAU Guidelines 2011 (updated 2013)

Relationship of 1973 WHO to 2004 WHO/ISUP

WHO 1973		WHO 2004
Papilloma	→	Papilloma
PUNLMP	→	Grade 1
	⇢	Grade 2
Low grade	→	Grade 2
	⇢	Grade 3
High grade	→	Grade 3

Am J Surg Pathol 22:1435, 1998
Eur Urol 46:170, 2004

www.pathology.jhu.edu/bladder

Relationship of WHO 1973 and 2004 WHO/ISUP Grade to Progression

WHO	Cases (%)	Progression (%)	
		45 mo	90 mo
Papilloma	5.2	0	0
G1	31.3	11	11
G2	59	11	24
G3	4.5	60	60

WHO/ ISUP	Cases (%)	Progression (%)	
		45 mo	90 mo
Papilloma	2.2	0	0
LMP	21.6	8	8
Low grade	54.5	10	13
High grade	**21.6**	**23**	**51**

Samaratunga H and Epstein JI, Urology 60: 315, 2002

Risk Stratification
Recurrence and Progression Risk

	Recurrence (%)		Progression (%)	
Risk group	1yr	5yr	1yr	5yr
Low	15	31	0.2	0.8
Intermediate	24-38	46-62	1-5	6-17
High	61	78	17	45

CIS – TICE Induction + Monthly Maintenance for 12 mos.

TABLE I: THE RESPONSE OF PATIENTS WITH CIS BLADDER CANCER IN SIX IND STUDIES

	Entered	Evaluable	CR	CRNC	Overall Response
No. (%)Of Patients	153	119 (78%)	54 (46%)	36 (30%)	90 (76%)

A 1989 update of these data is presented in Table II. The median duration of follow-up was 47 months.

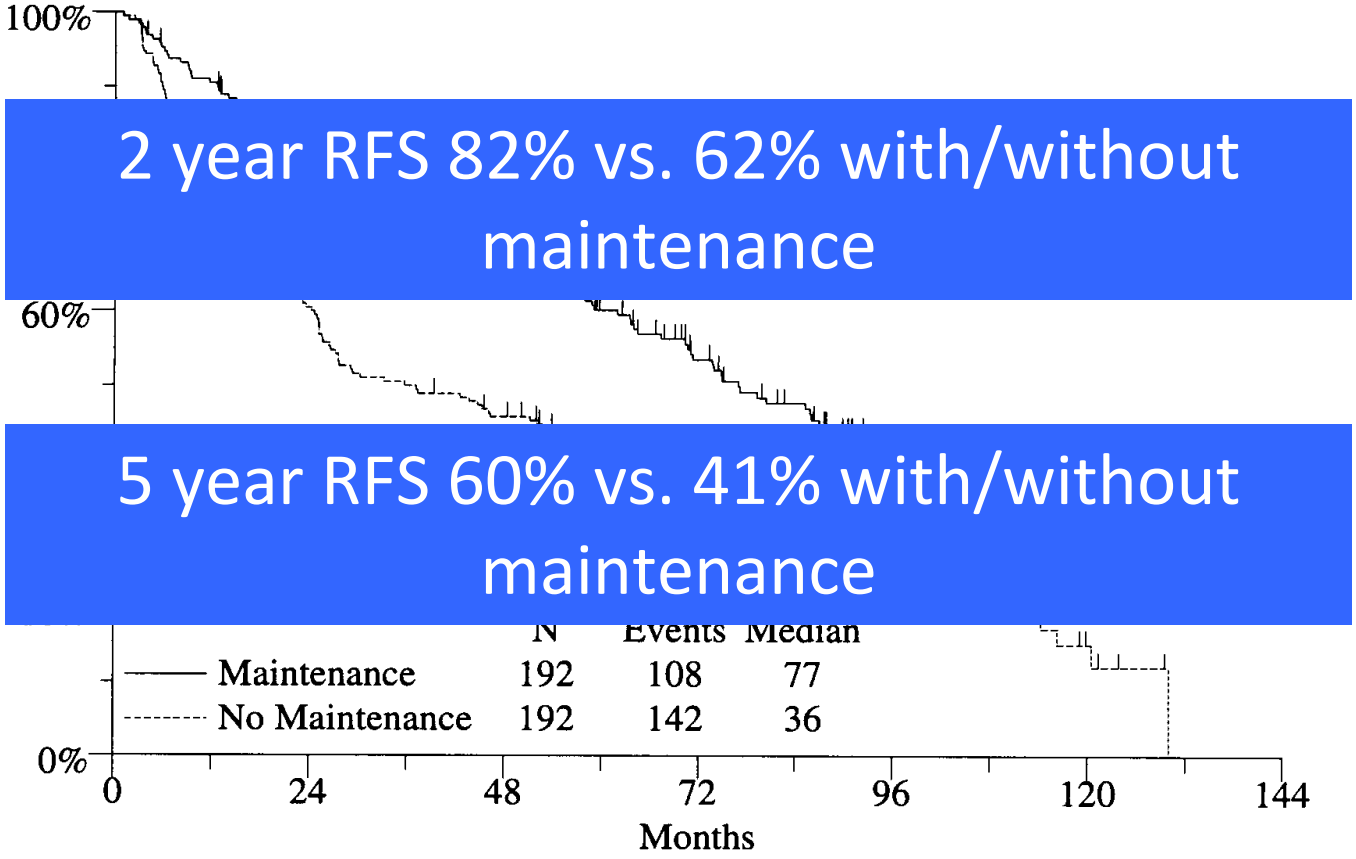
TABLE II: FOLLOW-UP RESPONSE OF PATIENTS WITH CIS BLADDER CANCER IN SIX IND STUDIES

	1989 Status of 90 Responders (CR or CRNC)			
	1987/CR	1987/CRNC	1987 Response	
Response	n = 54	n = 36	n = 90	Percent
CR	30	15	45	50
CRNC	0	0	0	0
Unrelated Deaths	6	6	12	13
Failure	18	15	33	37

Standard of Care

SWOG 8507 - BCG Maintenance

Recurrence-Free Survival



2 year RFS 82% vs. 62% with/without maintenance

5 year RFS 60% vs. 41% with/without maintenance

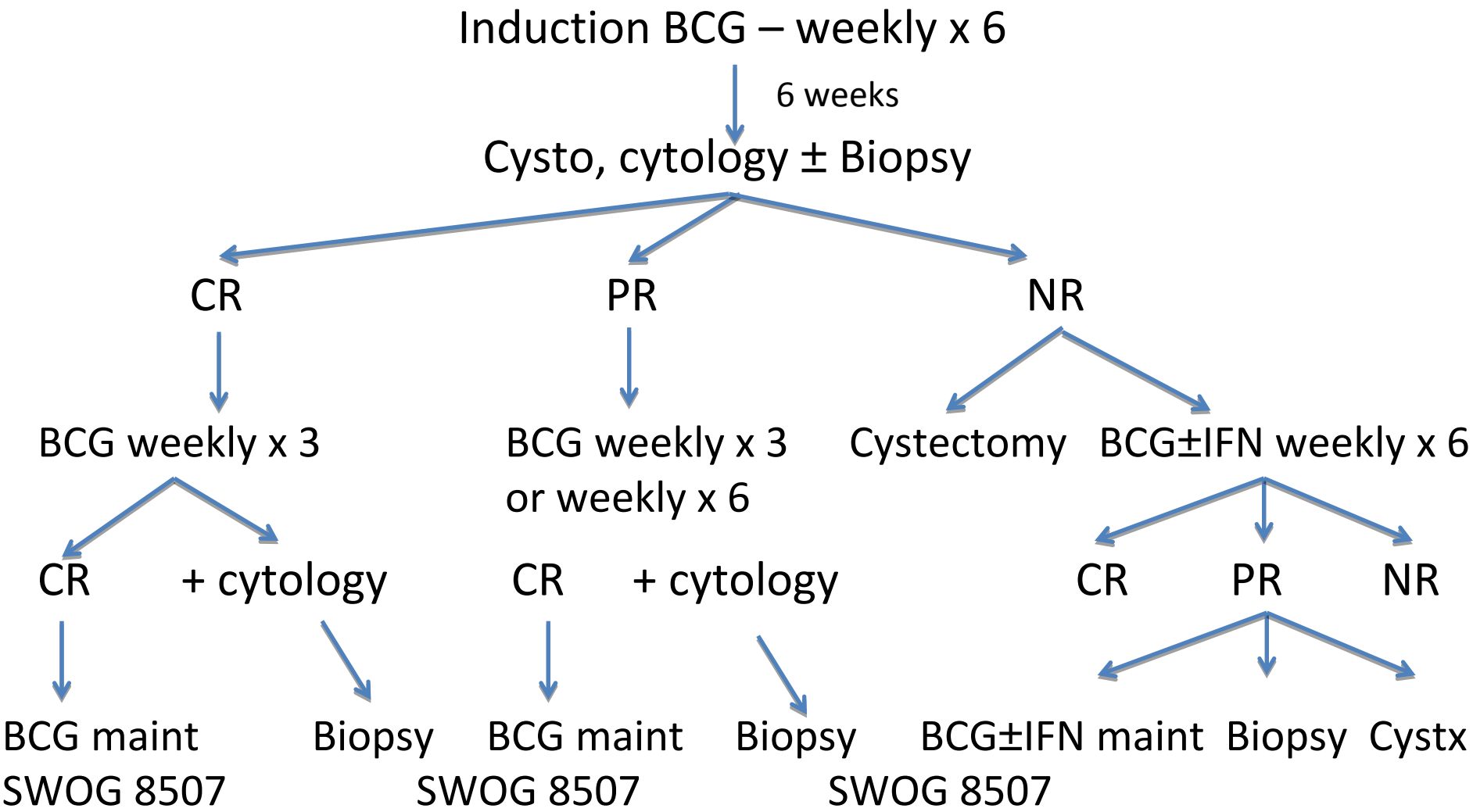
Lamm, DL et al, J Urol 163:1124, 2000

Intermediate Risk

- EORTC 30962 – patients with Ta, T1 disease do not benefit form more than one year of maintenance when using full dose BCG
  - HR = 0.88, 95%CI = [0.64, 1.21], p = 0.4380
- EORTC 30911 – BCG induction +3yr maintenance superior to Epirubicin
  - 0.59 (0.45–0.76) <0.001

CR: neg cysto/cytology
PR: neg cyto/+ cytology
NR: + biopsy

Algorithm



BCG - Facts

- 6-week induction course superior to TURBT alone for Ta, T1 and CIS (Level 1B)
  - Initial CR - 50-70%
- Second 6-week course [1,2] (Level 3)
  - Salvage additional 10-22%
- Maintenance therapy rationale
  - Repeated stimulation of immune system
  - Can give too much BCG - cytokine response with second 6 week course peaks by week three and may be suppressed during weeks 4-6.

[1] Catalona, et al J Urol 137:220-4, 1987
[2] Bui,Schellhammer Urology 49:687-90, 1997

BCG - Facts

- CIS ± Ta, T1 (SWOG 8507) (Level 1B)
  - 3 month CR with Induction alone 56%
  - 6 month CR with Induction alone 68%
  - 6 month CR 6 +3 84%
- Full dose BCG + 3 yrs maintenance optimal therapy for high risk disease (EORTC 30962) (Level 1B)
- BCG superior to MMC (Level 1A) and Epirubicin (Level 1B) only when maintenance therapy used[1,2]

[1] Sylvester, et al J Urol 174:86, 2005
[2] Malmstrom, et al Eur Urol 56:247, 2009

BCG - Facts

- Can re-induce CR with BCG in late relapsers (> 1 year)
- Randomized phase II trials to date testing a second induction course of BCG alone in patients who have failed one induction course
  - 2 yr RFS 3% vs 19% for Gemcitabine (Level 2B)[1]
- Patients with CIS who have failed 2 courses of BCG should not be treated with a 3rd course (Level 2B) [2]

[1] DiLorenzo et al Cancer 116:1893, 2010
[2] Rosevear, JUrol 186:817, 2011

What is the Effect Size for BCG?

Phase III RCT

- Recurrence with TURBT vs. TURBT + BCG

Author (yr)	No. Pts	TURBT (%)	TURBT+BCG (%)	P val	RR	RFS
Lamm ('80)	37	42	17	0.01	✔	
Lamm ('85)	57	52	20	<0.001	✔	✔
Herr ('85) 57% CIS	86	95	42	<0.001	✔	✔
Herr ('86) CIS+TaT1	49	100	35	<0.001	✔	✔
Yamamoto ('90)	44	67	17	<0.05	✔	
Pagano ('91)	133	83	26	<0.001	✔	
Melekos ('93)	94	59	32	<0.02	✔	
Krege ('96)	224	46	26	<0.05		✔ 3 yr

Adapted from Pinke, Lamm Textbook of Bladder Cancer, 2006

Potential Confounders in Summary Data of BCG vs TURBT alone (8 trials)

- Six trials used Pasteur strain
  - 75mg (1) 120mg (4) 150mg (1)
  - Tokyo strain, Connaught (120mg)
- Four trials used intravesical + percutaneous BCG
- Included low, intermediate and high risk groups
- Second induction (1) or Maintenance (4) BCG
- Endpoints mixed: recurrence rate vs. RFS at different time points