



Intravesical  
Chemotherapy  
for Bladder  
Cancer



# BCG Maintenance Should Be Less Intense



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# The Emperor's New Clothes



# Introduction

- Since the first report of intravesical BCG in 1976, BCG has been established as the standard of care for high-risk NMIBC
- Most guidelines recommend BCG maintenance for 1–3 years, whereas others include maintenance in a spectrum of options along with induction

Morales A, et al. J Urol 1976; 116:180

Babjuk M, et al. Eur Urol 2011;59:997

Chang SS, et al. [auanet.org](http://auanet.org) 2016

Montie JE et al. JNCCN 2009;7:8

# Limitations of Data: Maintenance BCG

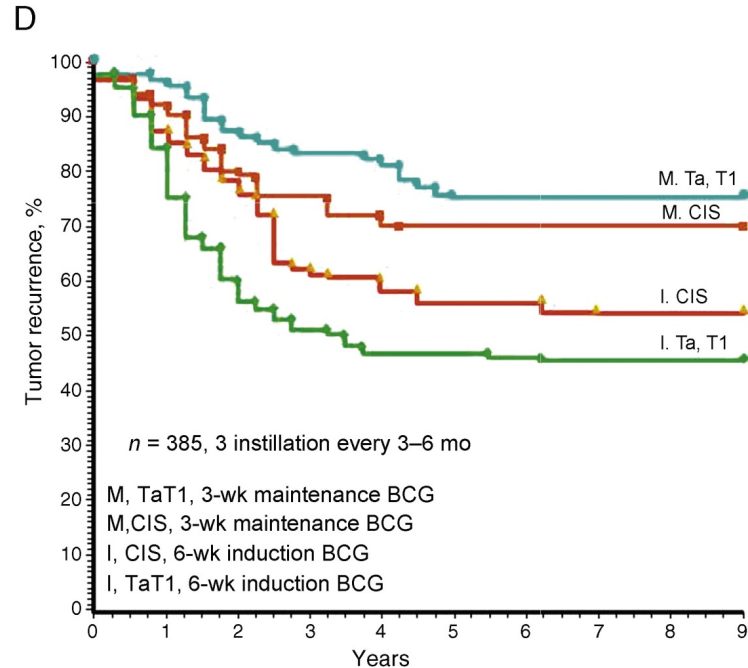
- Individual RCTs that directly compared BCG induction plus maintenance to BCG induction alone do not provide convincing evidence to support maintenance
- Recommendations for maintenance largely based on indirect comparisons in meta-analyses that suggest maintenance is more effective than induction alone, both for reducing recurrences and delaying progression

# Fly in the Ointment (or Instillations...)

- RCT's are for the most part underpowered
- Lack of good quality, “individual patient data” with long-term F/U makes direct comparisons difficult
- Meta-analyses: Indirect comparisons carried out
- Wide variations in the “Quality of TUR”
- No use of enhanced imaging with blue light or NBI
- BCG retreatment for relapse after induction unknown

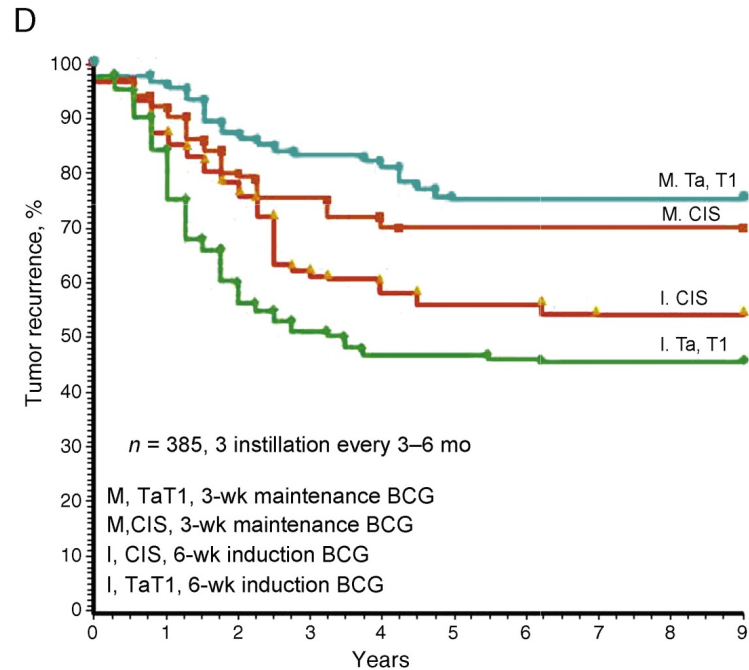
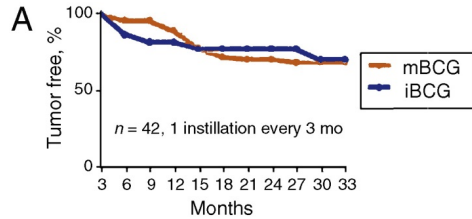
# BCG Maintenance: Not Created Equal

Only SWOG protocol shows benefit



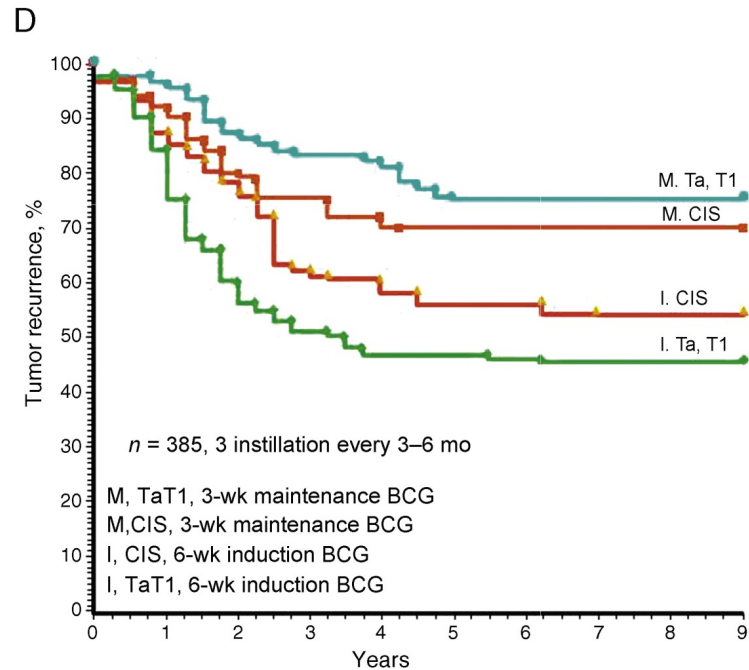
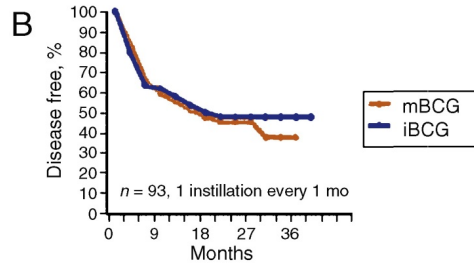
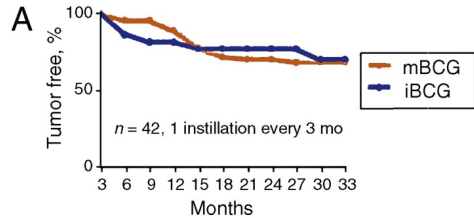
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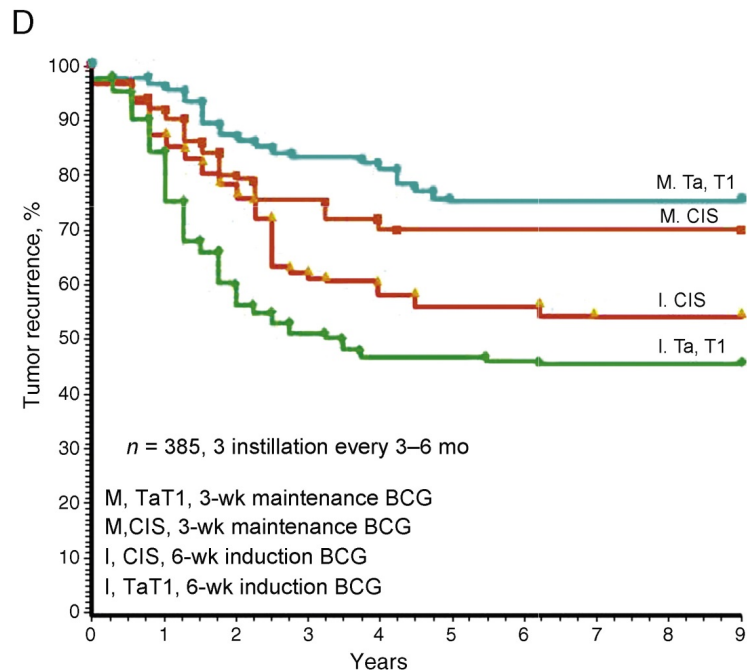
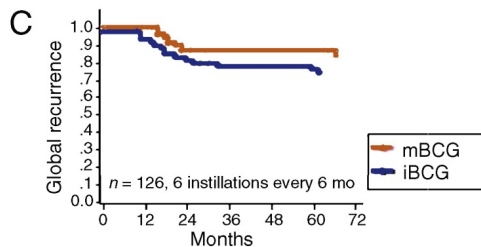
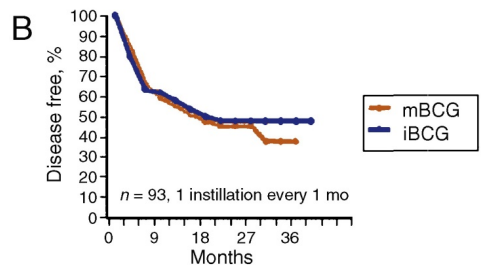
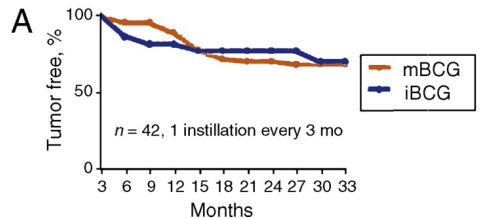
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# BCG Maintenance: Not Created Equal

Only SWOG protocol shows benefit



# What's the Evidence: RCT's

- Seven RCT's compared induction BCG + maintenance to induction alone, with or without retreatment with BCG on recurrence
- All but one of these studies were underpowered
- The largest study (SWOG) used a broad, composite end point: worsening-free survival

Ehdaie A, et al. Eur Urol 2013;64:579

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

# What's the Evidence: Meta-analyses

- 7 meta-analyses have been conducted, 3 included data from observational cohort studies
- Demonstrated benefit of maintenance BCG to reduce disease recurrence and delay progression compared to various control groups
- However, the analyses were based on suboptimal data
- Although there is new evidence that 1 year of maintenance BCG is sufficient treatment in intermediate-risk patients, the optimal duration of BCG maintenance remains unknown

**Table 1 – Randomized studies comparing bacillus Calmette-Guérin induction plus maintenance to induction alone**

Study	Inclusion criteria	Maintenance regimen	Median follow-up	Induction alone	Induction and maintenance	Patients, n	Recurrence, no.	Progression, no.
Badalament et al. [8]	Recurrent Ta, T1, CIS NMIBC	Monthly 2 yr	Overall: 22 mo	46	47	93	Maintenance: 23	Maintenance: 12
Hudson et al. [10]	Primary or recurrent Ta, T1, and CIS NMIBC	3 monthly 2 yr	Maintenance: 14.1 mo (mean)	21	21	42	Induction alone: 25 Maintenance: 5	Induction alone: 9 Unknown
Akaza et al. [9]	Recurrent Ta or T1 NMIBC	Monthly 1 yr	Induction alone: 12.3 mo (mean) Maintenance: 12.3 mo (mean)	21	21	42	Induction alone: 6 Maintenance: 5	Maintenance: 5
Lamm et al. [5]	Recurrent Ta or T1 (2 tumors within 1 yr or 3 recurrences in recent 6 mo), CIS	3 instillations at 3, 6, 12, 18, 24, 30, 36 mo	Induction alone: 12.3 mo (mean) Maintenance: 12.3 mo (mean)	21	21	42	Induction alone: 6 Maintenance: 5	Induction alone: 5 Maintenance: 87
Palou et al. [11]	Primary or recurrent Ta or T1 grade 3 or isolated CIS, or CIS with grade 2 NMIBC	6 weekly every 6 mo 2 yr	Induction alone: 12.3 mo (mean) Maintenance: 12.3 mo (mean)	21	21	42	Induction alone: 6 Maintenance: 5	Induction alone: 102** Maintenance: 2
Koga et al. [7]	Primary or recurrent Ta, T1, or CIS. (Ta and T1: not completely resectable by TUR)	3 monthly 1 yr	Induction alone: 64 mo Maintenance: 26.5 mo	27	24	51	Induction alone: 10 Maintenance: 1	Induction alone: 3 Maintenance: 0
Hinotsu et al. [6]	Recurrent Ta or T1 NMIBC: (a) the presence of ≥3 tumors (b) 2 prior recurrences or (c) recurrent tumor within 12 mo	3 instillations at 3, 6, 12, 18 mo	No maintenance: 28.7 mo Not reported	42	41	83	Induction alone: 7 Maintenance: 5	Induction alone: 1 Maintenance: 0
Total				444	442	886	Induction alone: 14 Maintenance: 355	Induction alone: 3 40 + 189*

The maintenance schemes varied from one instillation every 3 months during 1 year (4 instillations) to 21 instillations over 3 years

CIS = carcinoma in situ; NMIBC = non-muscle invasive bladder cancer; TUR = transurethral resection.

\* Recurrent cases and other causes of deaths.

\*\* Worsening-free survival.

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Akaza et al. [9]					52	107	Induction alone: 6 Maintenance: 22	Maintenance: 5
Lamm et al. [5]					192	384	Induction alone: 20 Maintenance: 108*	Induction alone: 5 Maintenance: 87
Palou et al. [11]					68	126	Induction alone: 142* Maintenance: 16	Induction alone: 102** Maintenance: 2
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Enrollment in the 7 studies ranged from 42 to 384 patients, for a total of 886 patients

Of this total, 355 patients had disease recurrence and in 229, disease progressed

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Koga et al. [7]	Primary or recurrent Ta, T1, or CIS. (Ta and T1: not completely resectable by TUR)	3 monthly 1 yr	Induction alone: 84 mo Maintenance: 26.5 mo	27	24	51	Induction alone: 10 Maintenance: 1	Induction alone: 3 Maintenance: 0
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Concerning recurrence, 3 of 7 studies found absolutely no evidence of a clinical benefit of maintenance BCG therapy

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Concerning recurrence, two studies reported nonsignificant trends in favor of maintenance

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<b>Total</b>				<b>444</b>	<b>442</b>	<b>886</b>	<b>Induction alone: 14 Maintenance: 355</b>	<b>Induction alone: 3 40 + 189*</b>

Concerning recurrence, only two studies reported significant differences in favor of maintenance

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Only one study (Lamm et al.) demonstrated a reduction in disease progression with maintenance, but progression was defined as a broad, composite end point: worsening-free survival

The term worsening-free survival was defined as death due to any cause, stage T2 or higher, or initiation of a change in treatment implying impending progression or disease worsening, such as cystectomy, systemic chemotherapy, and radiation tx

\*\* Worsening-free survival

# SWOG Maintenance Study

- 3-yr maintenance BCG is largely based on this study
- 19% advantage in 5-yr RFS (41% to 60%) and improvement of 6% in the 5-yr worsening-free survival (70% to 76%) favoring maintenance BCG (  $p = 0.04$  )
- However, the results of this study should be viewed cautiously given the contemporary statistical and methodological standards in conducting clinical trials

# Criticism #1: SWOG Maintenance Study

- For RFS, deaths prior to recurrence were counted as an event
- Death without recurrence was reported in 49 of 250 RFS events
- Thus, 1/5 of cases counted as recurrences were actually deaths
- In a comorbid population exposed to toxic therapy, deaths prior to recurrence will affect reported median duration of RFS, progression (worsening)-free survival, and disease-specific survival
- These limitations would have been addressed if the authors had carried out a proper competing-risks analysis

## Criticism #2: SWOG Maintenance Study

- The end point: worsening-free survival comprised several components (progression, change in treatment, death); however, the frequencies were not reported and likely significant variability exists for choosing to start tx or not
- It is unknown how many patients restarted BCG treatment after a NMIBC recurrence in the “no-maintenance” arm
- Death due to any cause is a problematic end point for a comorbid bladder cancer cohort

## Criticisms #3: SWOG Maintenance Study

- A one-sided test for significance was used, thus setting a low threshold to demonstrate a significant outcome
- Doubling the p values achieves a two-sided test and worsening-free survival fails to remain statistically significant, with a two-sided p value of 0.08
- If a significant difference is not achieved among the 384 patients analyzed, then the clinical benefit of exposing patients to long-term toxic therapy can be questioned

## Criticisms #4: SWOG Maintenance Study

- Finally, 30% (166/550) randomized patients were excluded after randomization based on “evidence of disease at randomization following induction therapy,” and the impact of this on the outcomes is unknown
- The distribution of tumor characteristics prior to induction BCG, such as tumor stage and grade are not listed
- Thus, the methodology does not conform to current, good statistical practice

# BCG Toxicity

- The downsides of indiscriminately adopting 3 years of maintenance BCG are **toxicity and compliance**
- Approximately 50% of patients treated by BCG complain of side effects
- Importantly, 5% were determined to be serious adverse events

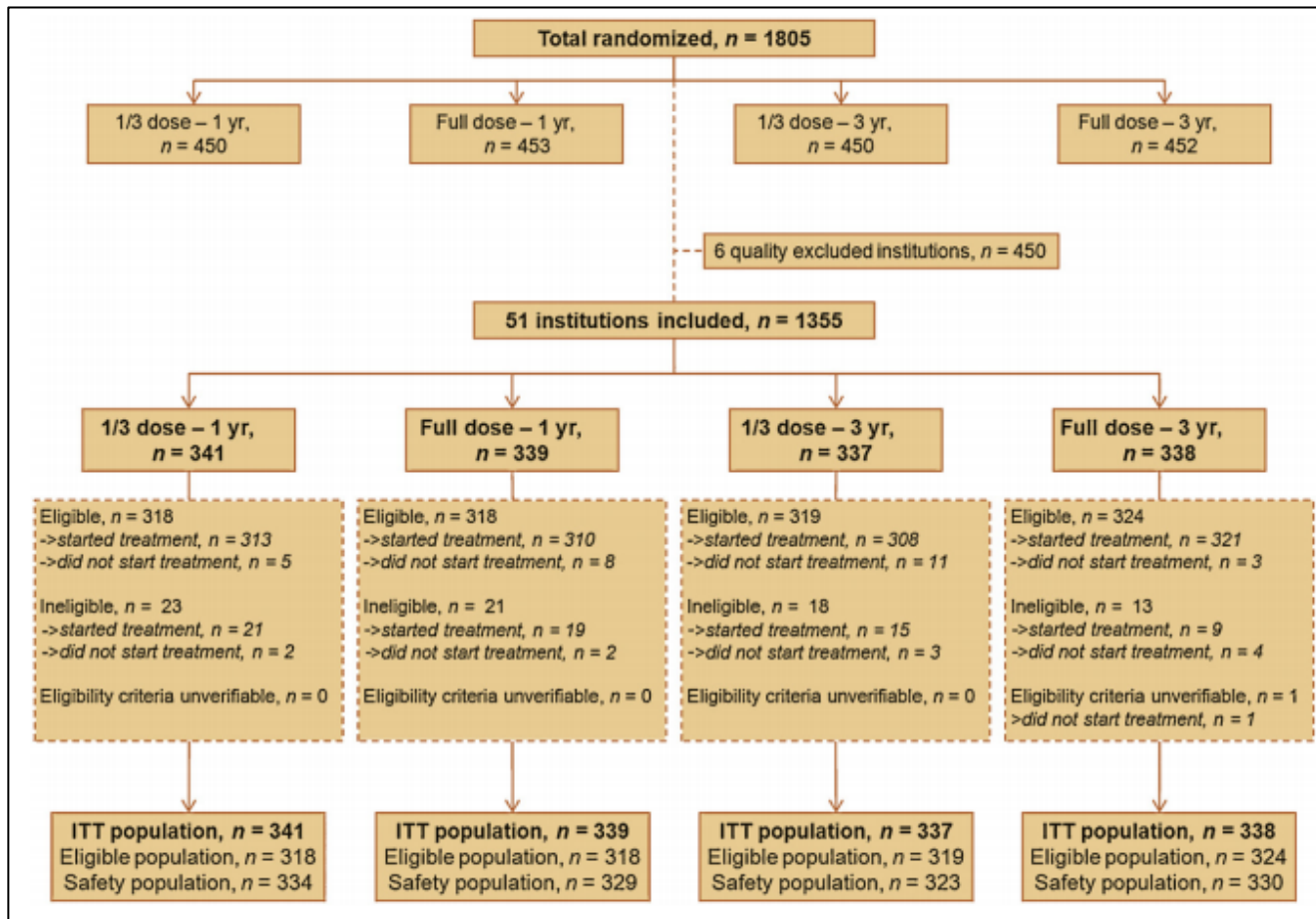
# BCG Toxicity

- Toxicity contributes to low compliance
- Only 16% of maintenance patients received all 8 scheduled tx's over a 3-year period in SWOG RCT
- A more recent EORTC study, 25% of the patients completed all 3 year of treatment, with 19% of the BCG patients stopping treatment for toxicity



# Optimal Duration of Therapy

- EORTC Trial compared 1 yr of maintenance to 3 yr of maintenance in intermediate- and high-risk patients
- No differences in terms of progression or death; however, **3 yr of maintenance reduced recurrences as compared to 1 yr in the high-risk patients but *not* in the intermediate-risk patients, showing that not all patients need to be treated with 3 yr of maintenance**



## Final Results of an EORTC-GU Cancers Group Randomized Study of Maintenance Bacillus Calmette-Guérin in Intermediate- and High-risk Ta, T1 Papillary Carcinoma of the Urinary Bladder: One-third Dose Versus Full Dose and 1 Year Versus 3 Years of Maintenance

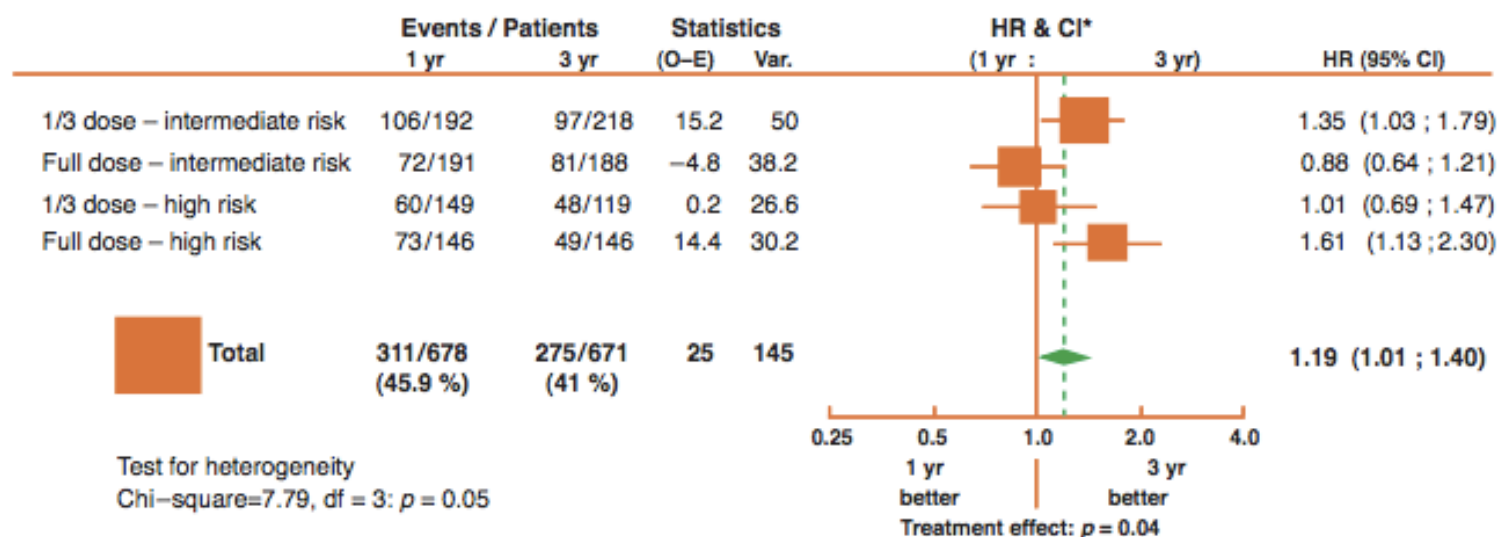


Fig. 5 – Disease-free interval: 1 yr of maintenance versus 3 yr of maintenance according to dose and risk group. HR = hazard ratio; CI = confidence interval; df = degrees of freedom.

# Summary: Against 3 Yr Maintenance Therapy

- Quality of TUR represents a major limitations of trials
- Studies carried out prior to the use of more modern practices such as an immediate postop instillation of chemotherapy, repeat TUR, and blue-light cystoscopy, all of which may decrease the rate of recurrence rates
- The therapeutic value of additional years of maintenance BCG compared to limited maintenance BCG or induction therapy followed by retreatment on recurrence should be weighed against the risks of adverse events and added cost

# Conclusion

- The optimal duration of BCG treatment in patients with NMIBC remains unknown and further studies are needed
- In addition to 3 years of maintenance BCG, guideline panels include 1 year of BCG maintenance and induction BCG with retreatment on recurrence as a possible treatment options, especially for intermediate risk
- Alternatives to 3 year maintenance should have lower level of evidence and grade of recommendation

# 3 Years of BCG Maintenance is Too Intense!



Are We Looking at the Emperor's New Clothes?