T1HG Bladder Cancer
What is the “Best” Therapy?

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Guidelines for T1HG Bladder Cancer

- **AUA**
  - Recommendation: BCG induction and maintenance
  - Option: Cystectomy

- **EAU**
  - Grade A: Full-dose intravesical BCG for 1–3 yr
  - Grade C: immediate cystectomy for highest risk of progression
• Five-year rate of progression: 21%
• Cancer-specific survival: 87%
• This included patients who did NOT received BCG
• Patients not receiving BCG had a 78% higher hazard for progression p<.001

Martin-Doyle....Bellmunt, JCO, 2015
Prognostic Factors and Risk Groups in T1G3 Non–Muscle-invasive Bladder Cancer Patients Initially Treated with Bacillus Calmette-Guérin: Results of a Retrospective Multicenter Study of 2451 Patients

T1HG patients treated with BCG

- Individual patient data for 2451 T1G3 patients
- Median follow-up of 5.2 yr
- 81% patients did NOT progress
- 79% did not need a radical cystectomy
- 91% disease specific survival

- Despite: reTUR only in 38%; BCG maintenance only in 38% (defined as > 6 instillations)

Gontero .... Palou, Eur Urol 2015
Reported reasons why BCG not used

1. “I’m not convinced it works” or “BCG does not affect progression”

2. “I don’t know what schedule to use”

3. “Treatment is too toxic for my patients”

4. “Clinical staging is inadequate” or “I fear LVI, variant histology, etc”

5. “Have Robot … must operate”
Platinum Opinion

Myths and Mysteries Surrounding Bacillus Calmette-Guérin Therapy for Bladder Cancer

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#1

BCG does not reduce progression rates

“I’m not convinced” or “the benefit is too small”
### Intravesical BCG

**Analysis of Progression in 20 Controlled Trials**

| Study Publ Year | Author and Group | Events / Patients | Statistics (O-E) | Var. | OR & CI (BCG / No BCG) | \( | 1-OR | % \ ± SD |
|-----------------|------------------|-------------------|------------------|------|------------------------|----------------|
| 1991            | Pagano (Padova)  | 11 / 63 3 / 70    | -4.4             | 3.1  |                        |                |
| 1987            | Badalament (MSKCC)| 6 / 46 6 / 47     | -0.1             | 2.6  |                        |                |
| 2000            | Lamm (SW8507)    | 102 / 192 87 / 192| -7.5             | 24.1 |                        |                |
| 2001            | Palou            | 2 / 61 3 / 65     | 0.4              | 1.2  |                        |                |
| 1996            | Rintala (Finnbl 2)| 3 / 90 3 / 92     | 0                | 1.5  |                        |                |
| 1995            | Rintala (Finnbl 2)| 4 / 40 2 / 28     | -0.5             | 1.3  |                        |                |
| 1995            | Lamm (SW8795)    | 24 / 186 15 / 191| -4.8             | 8.8  |                        |                |
| 1999            | Malmstrom (Sw-N) | 22 / 125 15 / 125| -3.5             | 7.9  |                        |                |
| 2001            | Nogueira (CUETO) | 8 / 127 10 / 247  | -1.9             | 3.9  |                        |                |
| 1991            | Rintala (Finnbl 1)| 2 / 58 3 / 51     | 0.7              | 1.2  |                        |                |
| 2001            | de Reijke (EORTC)| 18 / 84 10 / 84   | -4               | 5.9  |                        |                |
| 2001            | vd Meijden (EORTC)| 19 / 279 24 / 558| -4.7             | 9.1  |                        |                |
| 1982            | Brosman (UCLA)   | 0 / 22 0 / 27     | 0                | 0    |                        |                |
| 1990            | Martinez-Pineiro | 4 / 109 1 / 67    | -0.9             | 1.2  |                        |                |
| 1999            | Witjes (Eur Bropir)| 2 / 25 1 / 28    | -0.6             | 0.7  |                        |                |
| 1997            | Jimenez-Cruz     | 7 / 61 6 / 61     | -0.5             | 2.9  |                        |                |
| 1994            | Kalbe            | 2 / 35 0 / 32     | -1               | 0.5  |                        |                |
| 1991            | Kalbe            | 2 / 17 0 / 21     | -1.1             | 0.5  |                        |                |
| 1993            | Melekos (Patras) | 7 / 99 2 / 62     | -1.5             | 2    |                        |                |
| 1988            | Ibrahiem (Egypt) | 12 / 30 5 / 17    | -1.1             | 2.6  |                        |                |

**Total** 257 / 1749 196 / 2065 -36.8 80.9

Test for heterogeneity: \( \chi^2 = 9.73, df=18: p=0.9 \)

**Treatment effect:** \(p=0.00004\)

27% ±9 reduction

Sylvester, 2002
EORTC 30911
3 Week Maintenance BCG vs Epirubicin

**Rec reduced** with BCG Maintenance \((p<0.0001)\)

**Mets reduced** with BCG Maintenance \((p=0.046)\)

**Overall survival** (& DSS)
Improved with BCG Maint. \((P=0.023)\)

837 of 957 randomized pts without CIS followed for 9.2 yrs.
497 *intermediate* risk pts with as good or better benefit vs high risk

International Bladder Cancer Group (IBCG)

Defining and Treating the Spectrum of Intermediate Risk Nonmuscle Invasive Bladder Cancer

How many of the following 4 factors does the patient have?
- Multiple tumors
- Tumor size >3 cm
- Early recurrence (< 1 year)
- Frequent recurrences (>1 per year)

**0**
TREAT SIMILAR TO LOW RISK:
- TURBT + single immediate post-op chemotherapeutic dose, or
- Consider office fulguration and observation
- Consider intravesical chemotherapy

**1-2**
TREAT AS INTERMEDIATE RISK:
- TURBT plus adjuvant intravesical therapy (options include chemotherapy or BCG with maintenance [full dose, 1 year])

**≥3**
TREAT AS HIGH RISK:
- TURBT + BCG induction + maintenance

Kamat et al, J Urol, 2014
“We don’t know what schedule to use”
“I’m confused about maintenance .... does it really work?”
BCG Maintenance: Not Created Equal
Only SWOG protocol shows clear benefit

Kamat & Porten, Eur Urol, 2014
BCG Maintenance: **Not Created Equal**

Only SWOG protocol shows clear benefit
#3

“Treatment is too toxic for my patients”

“Most patient cannot tolerate full course of BCG”
BCG is well tolerated

EORTC 30962
• Comparison of full dose vs 1/3^{rd} dose BCG for 1 year vs 3 years
  • 1355 patients; median follow-up of 7.1 yrs,
• <10% patients discontinued due to toxicity

International IPD Survey
• 971 patients
  • only 5.2% discontinued BCG maintenance due to toxicity.

Strategies for Optimizing Bacillus Calmette-Guérin

Jay B. Shah, MD, Ashish M. Kamat, MD

• Minimize fluid intake before instillation
• Start with empty bladder
• Inspect voided urine for visible hematuria
  • (routine urinalysis/dipstick not necessary)
• Catheterize atraumatically
• Minimize lubricant (to avoid BCG clumping)
• Avoid lidocaine (acidity degrades BCG)

• No rotisserie-style turning
• Statins/aspirin therapy okay
• Antispasmodics for local symptoms
• Antipyretics for influenza-like symptoms
• Give 1 dose of quinolone 6 hours after BCG
• Suspected BCGosis/BCG sepsis needs prompt workup and aggressive therapy
“Clinical staging is inadequate”
“I fear LVI, variant histology, etc”
BCG Therapy is not a substitute for Bad Judgment
Rule out Variant Histology
MPBC Progresses with Intravesical BCG

- 89% recurred
- 67% progressed (median 8 mos)
- 6 (22%) metastatic disease

T1b Bladder Cancer

Benardini et al, J Urol, 2001; Also in Martin-Doyle, JCO, 2015
LVI in TURBT

LVI on TURBT associated with
- Lower 5-year DSS
  - 34% vs 63% (p=.027)
- Associated with understaging
  - LVI 75% vs 46% (p=.08)
  - 118 primary T1; LVI in 28%
  - Only risk factor independently associated with progression

Also seen in Martin-Doyle, JCO, 2015
“The Robot has made Radical Cystectomy Easy”

Robotic arm - for self congratulations
Options for T1 Bladder Cancer

- Option 1: Cystectomy
  - ‘Take it out, be done with it’ ... ‘Not my problem’

- Option 2: Intravesical BCG
  - Indiscriminate Use
  - Ad nauseum ... Natural Selection
Options for T1 Bladder Cancer

- Option 1: Cystectomy
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  - Indiscriminate Use
  - Ad nauseum ... Natural Selection

- Option 3: Intelligent Design
  ... personalized therapy ...
Most T1HG patients benefit from BCG (Induction and Maintenance)