# Non-muscle Invasive Bladder Cancer, including Chemoprevention ~ Review of Existing Guidelines & International Recommendations

*~ Donald L. Lamm, MD*

## Non-muscle Invasive Bladder Cancer: Review of Prevention, Treatment, and Guidelines

Don Lamm, M.D.

Clinical Professor of Urology,
University of Arizona, and
Director, BCG Oncology,
Phoenix, AZ

## Guidelines

- European Association of Urology (EAU) Guidelines on TaT1 (non-muscle invasive) Bladder Cancer (Babjuk M, et al., 2008)
- First International Consultation on Bladder Tumors (FICBT) (Soloway MS [Ed]., 2005)
- National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Bladder Cancer, including Upper Tract Tumours and Urothelial Carcinoma of the Prostate (NCCN, 2007)
- American Urological Association (AUA) Guidelines for the Management of Non-muscle Invasive Bladder Cancer (Stages Ta,T1, and Tis): 2007 Update (AUA, 2007; Hall MC, et al., 2007)
- Synthesis: International Bladder Cancer Group

**Current Approaches to the Management of NMIBC: Comparison of International Guidelines as Recommended by International Bladder Cancer Group.** Persad, R. Eur Urol. 2009.

- **Level of Evidence**
- 1a Evidence from meta-analysis of randomized trials
- 1b Evidence from at least one randomized trial
- 2a Evidence from a good controlled study without randomization
- 2b Evidence from a well-designed quasi-experimental study
- 3 Evidence from well-designed non-experimental studies, such as comparative studies, correlation studies and case reports
- 4 Evidence from expert committee reports or opinions or clinical experience of respected authorities
- **Grade: Nature of Recommendations**
- A Based on clinical studies of good quality and consistency addressing the specific recommendations and including at least one randomized trial
- B Based on well-conducted clinical studies, but without randomized clinical trials
- C Made despite the absence of directly applicable clinical studies of good quality

**Definitions**

| | Low-Risk | Intermediate-Risk | High-Risk |
|---|---|---|---|
| **EAU** | G1-2Ta | Mult G2Ta, G1T1, sol G2T1 | Mult G2T1, G3Ta-T1, CIS |
| **FICBT** | Low-grade Ta | Rec or mult Low Grade | High-grade Ta, all T1, CIS |
| **NCCN** | G1-2Ta | G3Ta, solitary G1-2T1 | Multifocal T1, G3T1 |
| **AUA** | Small, low-grade Ta | Mult or large low -grade Ta | High-grade Ta, all T1, CIS |
| **IBCG** | Sol low-grade Ta | Rec or mult low-grade Ta | All High grade, T1 and CIS |
| **Risk:** | **Rec: moderate Prog: low** | **Rec : mod to high Prog: low to mod** | **Rec: high Prog: high** |

## Treatment by Risk Category

- Low risk: Immediate postop chemotherapy. BCG is NEVER given immediately postop!
- Intermediate risk: Immediate postop chemo; chemotherapy x6 previously recommended. Now 3 wk. maintenance BCG: Level 1 evidence
- High Risk: BCG immunotherapy, cystectomy for failure

## Diet and Lifestyle BT Prevention

- Second hand smoke, pesticides, diesel fuel and organic chemical exposure, as well as excessive exposure to dyes should be avoided.
- Water reduces BT risk, but only if free of arsenic and insectacides.
- Fruit and vegetables: reduce carcinogenic DNA adducts in urine.
- Soy: genistein is excreted in the urine in active form and kills 7/8 human BT cell lines in vitro.
- Broccoli: only 3 servings a month reduced BT risk up to 50% in 3 independent studies.
- Garlic: randomized controlled murine trial in my lab demonstrated that oral garlic supplement signficantly reduced MBT2 growth and cancer death.
- High dose vitamins A, B6, C and E plus zinc significantly reduced BT recurrence (40%) in pts with suboptimal BCG, but not optimal maintenance.

Oral Allium sativum (AS) or BCG in Murine TCC: Incidence, Growth & Survival

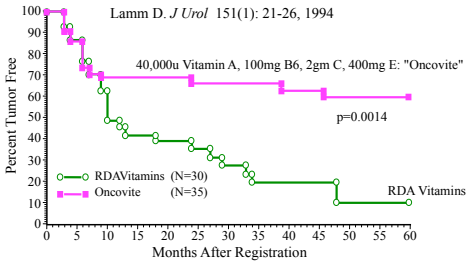
| Group | Inc d2 | Vol d35 | Survival d50 |
|---|---|---|---|
| Saline: | 18 (90%) | 4047 | 4 (20%) |
| BCG: | 3 (15%)*** | 390*** | 15 (75%)*** |
| AS5mg: | 17 (85%) | 4670 | 3 (15%) |
| AS50mg: | 14 (70%) | 2563** | 8 (40%) |
| AS 500mg: * | 12 (60%) | 1644*** | 10 (50%)* |

*P<.05; **P<.025; ***P<.001

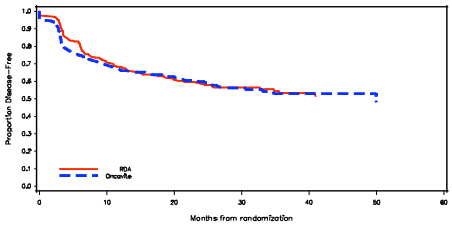
Lamm DL: J Nutr. 2001,131:1067S

**Kaplan Meier Estimate of 5 Year Tumor Free Rate**

In Patients Receiving Vitamin Supplement and BCG Therapy For Bladder Carcinoma




Efficacy Results – Disease Free Interval
BCG + RDA vs BCG + Oncovite




9

Comparison of Guidelines for Intermediate Disease

**EAU** (Multifocal G2Ta, G1T1, solitary G2T1)

- TURBT; Single, immediate post-operative instillation of chemotherapy followed by:
  - Induction BCG plus maintenance (at least 1 year) (grade A), or
  - Maintenance intravesical chemotherapy (grade A) of 6-12 months (grade B)

**FICBT** (Multiple low-grade Ta)

- TURBT; Single immediate post-operative instillation of chemotherapy
- Adjuvant intravesical therapy: First-line: intravesical chemotherapy < 6 months (grade B). Second-line: BCG (grade A)

**NCCN** (G3Ta, solitary G1-2T1)

- TURBT>Observe or Intravesical therapy
- BCG (preferred) (category 1) or Mitomycin (category 2A)

**AUA** (Multifocal and/or large volume low-grade Ta or recurrent low-grade Ta)

- TURBT, Intravesical BCG or mitomycin C (recommendation)
- Maintenance BCG or mitomycin (option)

**IBCG: 3 week maintenance BCG based on Level 1 evidence from EORTC**

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

## Comparison of Guidelines for High Risk Disease

**EAU** (Multiple G2T1, G3Ta–T1 )

- Repeat TURBT 2–6 weeks after initial resection (grade B)
- Intravesical BCG induction plus maintenance for at least 1 year (grade A)
- Immediate radical cystectomy for highest risk patients (grade A)
  - Multiple recurrent high-grade tumours
  - High-grade T1 tumours
  - High-grade tumours with concomitant CIS

CIS: Intravesical BCG plus maintenance for at least 1 year (grade A)

- Assess response at 3 months: If no response:
  - Continue with three weekly boosters (grade B), or
  - Additional 6-week course of BCG (grade B), or
  - Cystectomy (grade B)
- No complete response at 6 months: radical cystectomy (grade B)

## Comparison of Guidelines for High Risk Disease

**FICBT** (High-grade Ta; T1 or CIS)

- Second-look TURBT and bladder mapping biopsies in 2–4 weeks for Ta or T1 (grade B)
- If residual tumor is found: Re-resection and one immediate instillation of chemotherapy
  - Followed by 6-week BCG induction and 1–3 years of BCG maintenance (grade A)

**NCCN** (T1, G3)

- Complete Resection: BCG preferred (category 1) or mitomycin (category 2A); Consider cystectomy
- Uncertain Resection: Repeat resection or cystectomy
  - If positive: BCG (category 1) or cystectomy (category 2A)
  - If negative: BCG (category 1) or mitomycin (category 2A)
- Any CIS/Tis: Complete resection followed by intravesical BCG

**AUA and IBCG** (High-grade Ta, T1 and/or CIS)

- Repeat resection if lamina propria invasion without muscularis propria in specimen prior to intravesical therapy (standard)
- Induction BCG followed by maintenance (recommendation)
- Cystectomy (option)

## 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

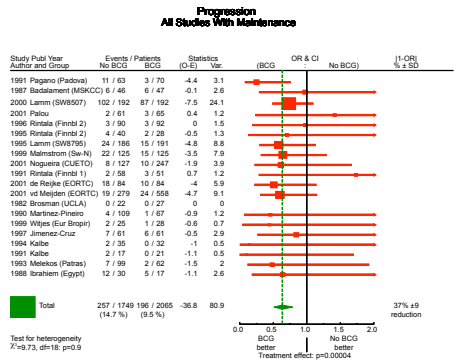
| Treatment | | Progression |
|---|---|---|
| • No BCG | | 304/2205 (13.8%) |
| • BCG | | 260/2658 ( 9.8%) |
| Difference | | 4.0% |
| Odds ratio (OR) | 0.73 | |
| Odds reduction | | 27% (95% CI: 11%–40%) |
| P Value | | 0.001 |

## Progression: Maintenance BCG

| Patients OR | | No BCG | BCG |
|---|---|---|---|
| No Maint 1.28 | 1049 | 10.3% | 10.8% |
| Maintenance 0.63 | 3814 | 14.7% | 9.5% |

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.




## Follow UP

- Follow-up: AUA recommends cystoscopy at 3 month intervals for 2 years, 6 month for 2 years, then annually, but for low grade, low risk patients this is excessive.
- EAU for low grade: cystoscopy at 3 months, and if negative at 9 months and then yearly for 5 years. But, risk for recurrence is lifelong and some would be missed after 5 years.

*Document*

# Non-muscle Invasive Bladder Cancer, including Chemoprevention ~ Review of Existing Guidelines & International Recommendations

*~ Donald L. Lamm, MD*

**Current Approaches to the Management of NMIBC: Comparison of International Guidelines as Recommended by International Bladder Cancer Group.** Raj Persad,[a] Donald Lamm,[b] Maurizio Brausi,[c] Mark Soloway,[d] Joan Palou,[e] Andreas Böhle,[f] Marc Colombel,[g] Hideyuki Akaza,[h] Roger Buckley[i] J Alfred Witjes[j]

[a]Department of Urology/Surgery, Bristol Royal Infirmary & Bristol Urological Institute, Bristol, United Kingdom
[b]Department of Surgery, University of Arizona; BCG Oncology, Phoenix, Arizona, USA
[c]Department of Urology, AUSL Modena Estense and B Ramazzini Hospitals, Modena, Italy
[d]Department of Urology, University of Miami School of Medicine, Miami, Florida, USA
[e]Department of Urology, Fundació Puigvert, Universitat Autònoma de Barcelona, Barcelona, Spain
[f]Department of Urology, HELIOS Agnes Karll Hospital, Bad Schwartau, Germany
[g]Department of Urology, Claude Bernard University, Hôpital Edouard Herriot, Lyon, France
[h]Department of Urology, University of Tsukuba, Tsukuba, Japan
[i]Department of Urology, North York General Hospital, Toronto, Ontario, Canada
[j]Department of Urology, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands

| Level | Type of Evidence |
|---|---|
| 1a | Evidence obtained from meta-analysis of randomized trials |
| 1b | Evidence obtained from at least one randomized trial |
| 2a | Evidence obtained from one well-designed controlled study without randomization |
| 2b | Evidence obtained from at least one other type of well-designed quasi-experimental study |
| 3 | Evidence obtained from well-designed non-experimental studies, such as comparative studies, correlation studies and case reports |
| 4 | Evidence obtained from expert committee reports or opinions or clinical experience of respected authorities |
| **Grade** | **Nature of Recommendations** |
| A | Based on clinical studies of good quality and consistency addressing the specific recommendations and including at least one randomized trial |
| B | Based on well-conducted clinical studies, but without randomized clinical trials |
| C | Made despite the absence of directly applicable clinical studies of good quality |

Guideline panels have used level of evidence standards similar to those above.

| | Definitions | | |
|---|---|---|---|
| | **Low-Risk** | **Intermediate-Risk** | **High-Risk** |
| **EAU** | G1-2Ta<br><br>Low risk of tumour recurrence and progression<br><br>(EORTC recurrence score = 0; progression score = 0) | Multifocal G2Ta, G1T1, solitary G2T1<br><br>Intermediate- or high-risk of recurrence and intermediate risk of progression<br><br>(EORTC recurrence scores ranging from 1–9; progression scores ranging from 1–6) | Multifocal G2T1, G3Ta-T1, CIS<br><br>High-risk of progression<br><br>(EORTC progression scores ranging from 7–23) |
| **FICBT** | Low-grade Ta | Low-grade Ta with high-risk factors for recurrence or recurrent low-grade Ta tumors | High-grade Ta, all T1, CIS |
| **NCCN** | G1-2Ta | G3Ta, solitary G1-2T1 | Multifocal T1, G3T1 (CIS listed separately) |
| **AUA** | Small volume, low-grade Ta | Multifocal and/or large volume low -grade Ta<br><br>High risk of recurrence, low risk of progression | High-grade Ta, all T1, CIS |

Panels recognize the importance of risk stratification. The most simple system, similar to that of the AUA, is to place all high grade tumors, all T1 tumors and all cases with CIS into the high risk group. Solitary/small volume low grade Ta tumors are low risk, and everything in between is intermediate risk.

Tumors are to be widely resected, with deep and wide margins that include muscle. CIS is resected/fulgurated completely and perforation avoided.

For **Low Risk Disease**: Immediate postoperative intravesical chemotherapy is recommended by all panels. Several randomized clinical trials have confirmed the benefit and Sylvester's meta-analysis shows a 39% risk reduction (Sylvester, 2004). **BCG is NEVER given immediately postoperatively.** Maintenance therapy, including BCG, has not been demonstrated to improve recurrence prevention. Panels agree that no chemotherapy has proven to be superior to other chemotherapies.

For **Intermediate Risk Disease:** Panels vary on recommendations for intermediate disease. All agree that adjuvant therapy is indicated. BCG or chemotherapy may be used, and there is no standard recommendation for dose or duration of treatment. All panels made recommendations before the results of the EORTC comparison of maintenance BCG using the SWOG 3 week

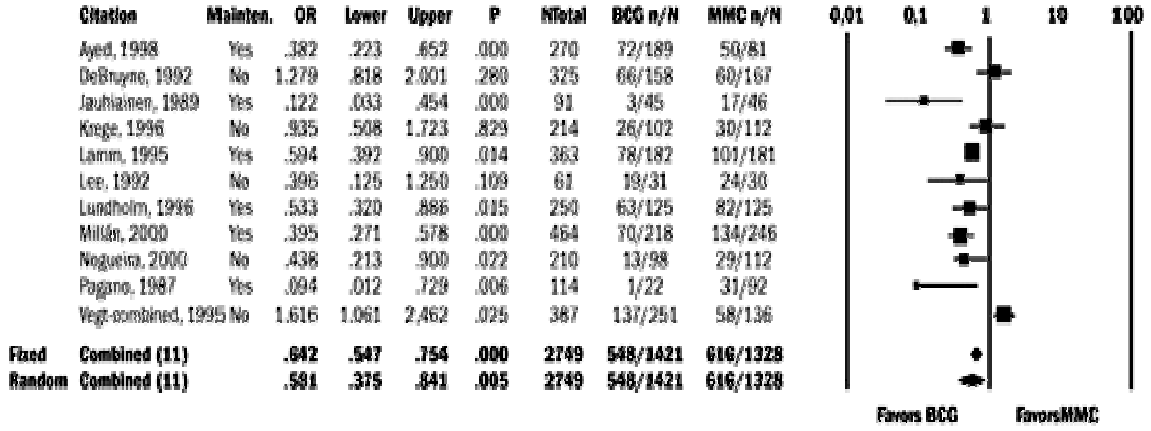
maintenance schedule versus induction Epirubicin. In that study of 957 intermediate risk patients followed for 9.2 years time to first recurrence ($p<0.0001$), time to distant metastases ($p=0.03$), and overall ($p=0.02$) and disease-specific survival ($p=0.03$) were all significantly prolonged with BCG compared to epirubicin (Sylvester RJ, et al., 2008). Considering the new level 1 evidence, the IBCG recommends 3 week maintenance BCG as the treatment of choice for intermediate risk bladder cancer. Chemotherapy remains an option for this group, and there is increasing use of maintenance schedules, though randomized trials are limited.

| Guideline | Definition of Intermediate Risk | Recommendations |
|---|---|---|
| **EAU** | Multifocal G2Ta, G1T1, solitary G2T1<br>Intermediate- or high-risk of recurrence and intermediate risk of progression<br>(EORTC recurrence scores ranging from 1–9; progression scores ranging from 2–6) | • TURBT<br>• Single, immediate post-operative instillation of chemotherapy followed by:<br>– Induction BCG plus maintenance (at least 1 year) (grade A), or<br>– Maintenance intravesical chemotherapy (grade A) of 6-12 months (grade B) |
| **FICBT** | Multiple low-grade Ta | • TURBT<br>• Single immediate post-operative instillation of chemotherapy<br>• Further adjuvant intravesical therapy:<br>– First-line: intravesical chemotherapy < 6 months (grade B)<br>– Second-line: BCG (grade A) |
| | Recurrent low-grade Ta | • Office fulguration only in select patients with < 5 small (< 0.5 cm) low-grade recurrent tumours and negative cytology (grade C)<br>• Formal TURBT if clinical doubt that tumour is low-grade, cytology positive, or change in tumour appearance has occurred (grade C)<br>• Adjuvant intravesical therapy (see above) |
| **NCCN** | G3Ta, solitary G1-2T1 | • TURBT>Observe<br>or<br>• Intravesical therapy<br>– BCG (preferred) (category 1)<br>or<br>– Mitomycin (category 2A) |
| **AUA** | Multifocal and/or large volume low-grade Ta or recurrent low-grade Ta<br>High risk of recurrence, low risk of progression | • TURBT<br>• Intravesical BCG or mitomycin C (recommendation)<br>• Maintenance BCG or mitomycin (option) |

EORTC: European Organization for the Research and Treatment of Cancer; TURBT: transurethral resection of the bladder tumour; EAU: European Association of Urology; FICBT: First International Consultation on Bladder Tumors; NCCN: National Comprehensive Cancer Network; AUA: American Urological Association

**High Risk disease:** A single-arm meta-analysis of randomized controlled trials in high-risk patients conducted by the AUA confirms the superiority of maintenance BCG to mitomycin C with or without maintenance: the estimated five-year recurrence rate was 34% in patients receiving TURBT and BCG maintenance and 62% with mitomycin C maintenance. The meta-analysis of all risk groups found that, compared with TURBT and mitomycin C maintenance, TURBT and BCG maintenance therapy reduced recurrence by 17%. The AUA meta-analysis also found a trend to improvement in overall progression with BCG maintenance therapy compared to mitomycin C plus maintenance. (AUA, 2007; Hall MC, et al., 2007). Meta-analysis of 24 trials involving 4,863 patients showed that BCG maintenance therapy was associated with a 37% reduction in the risk of tumour progression compared to TURBT alone, TURBT plus intravesical chemotherapy, or TURBT plus another immunotherapy (Sylvester RJ, et al., 2002) Another meta-analysis of 11 clinical trials comparing BCG and mitomycin C showed that BCG was superior to mitomycin C in reducing tumour recurrence (odds ratio [OR] 0.56, 95% confidence interval [CI], 0.38 to 0.84, p=0.005; see Figure 2a). In the subgroup treated with BCG maintenance, all 6 individual studies showed a significant superiority of BCG over mitomycin C (OR, 0.43, 95% CI, 0.35 to 0.53, p<0.001; see Figure). (Böhle A, et al., 2003)

**Tumour recurrence (all studies) with odds ratio (OR) as effect size**. (Böhle A, et al., 2003)




MMC: mitomycin C; BCG: bacillus Calmette-Guérin; mainten: maintenance BCG therapy

Given these results, the EAU, FICBT, NCCN and AUA regard BCG as the standard adjuvant treatment for high-risk patients. There is no consensus on the optimal BCG maintenance schedule and differences exist among the four guidelines with regards to other options in high-risk patients. The EAU recommends repeat resection in 2-6 weeks and maintenance BCG for at least a year. The AUA recommends repeat resection if no muscle is present in the specimen, followed by maintenance BCG (preferred, category 1, or Mitomycin C). The other panel recommendations are listed below. Failure to achieve complete response in CIS, or recurrence of high grade, T1 disease after BCG is considered to be an indication for cystectomy.

| Guidelines | Definition | Recommendations |
|---|---|---|
| **EAU** | Multiple G2T1, G3Ta-T1<br><br>High-risk of progression<br><br>(EORTC progression scores ranging from 7–23) | • Repeat TURBT 2-6 weeks after initial resection (grade B)<br>• Intravesical BCG induction plus maintenance for at least 1 year (grade A)<br>• Immediate radical cystectomy for highest risk patients (grade A)<br>— Multiple recurrent high-grade tumours<br>— High-grade T1 tumours<br>— High-grade tumours with concomitant CIS |
| | CIS | • Intravesical BCG plus maintenance for at least 1 year (grade A)<br>— Assess response at 3 months:<br>▪ If no response:<br>• Continue with three weekly boosters (grade B), or<br>• Additional 6-week course of BCG (grade B), or<br>• Cystectomy (grade B)<br>— No complete response at 6 months: radical cystectomy (grade B) |
| **FICBT** | High-grade Ta | • Second-look TURBT and bladder mapping biopsies 2-4 weeks after initial resection (grade B)<br>• If residual tumour is found:<br>– Re-resection and one immediate instillation of chemotherapy<br>– Followed 2-3 weeks later by 6-week BCG induction and 1-3 years of BCG maintenance (grade A) |
| | T1 | • Repeat TURBT (grade B)<br>• Initial intravesical BCG for patients with completely resected primary and recurrent T1 tumours (based on a negative repeat resection) (grade C) |
| | CIS | • Intravesical BCG for 6 weeks (grade A)<br>• Maintenance BCG for ≥ 1 year (grade A) |
| **NCCN** | T1, G3 | *Complete Resection:*<br>• BCG preferred (category 1) or mitomycin (category 2A)<br>• Consider cystectomy<br>*Uncertain Resection:*<br>• Repeat resection or cystectomy<br>– If positive: BCG (category 1) or cystectomy (category 2A)<br>– If negative: BCG (category 1) or mitomycin (category 2A) |
| | Any CIS/Tis | • Complete resection followed by intravesical BCG |
| **AUA** | High-grade Ta, T1 and/or CIS | • Repeat resection if lamina propria invasion without muscularis propria in specimen prior to intravesical therapy (standard)<br>• Induction BCG followed by maintenance (recommendation)<br>• Cystectomy (option) |

Follow up regimens vary according the risk group. The AUA recommends cystoscopy at 3 month intervals for 2 years, 6 months for 2 years and yearly thereafter, but for low risk patients this appears to be excessive. The EAU recommends cystoscopy at 3 months, and if negative at 9 months and then yearly for 5 years. The risk for recurrence does continue beyond 5 years, so recurrence would be missed if follow up is stopped. Controlled trials do not exist, so firm recommendations cannot be made.