

Controversies in the management of Non-muscle invasive bladder cancer

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NCCN - Bladder Cancer

APPROXIMATE PROBABILITY OF RECURRENCE

| Pathology | Approximate Probability of Recurrence in 5 years |
|----------------------|--|
| Ta, low grade | 50% |
| Ta, high grade | 60% |
| T1, low grade (rare) | 50% |
| T1, high grade | 50% - 70% |
| Tis | 50% - 90% |

NCCN, National Comprehensive Cancer Network.
NCCN. Bladder Cancer Guidelines.



AUA/SUO Risk Stratification 2016

| Low Risk | Intermediate Risk | High Risk |
|--|---|------------------------------------|
| LG solitary Ta <3cm, initial or recurrent > 1 year since prior tumor | LG Ta > 3cm, multifocal, or recurrent within 1 year | HG T1 |
| PUNLMP | LG T1 | CIS |
| | Initial HG Ta < 3cm | HGTa >3cm, multifocal or recurrent |
| | | Recurrent HGTa after BCG |
| | | Any variant histology |
| | | LVI |

Controversies

- **Low grade disease**
 - Immediate post-TUR instillation (is Mitomycin dead?)
 - **Office fulguration**
 - Flexible blue light cystoscopy facilitate office management?
 - **Surveillance?**

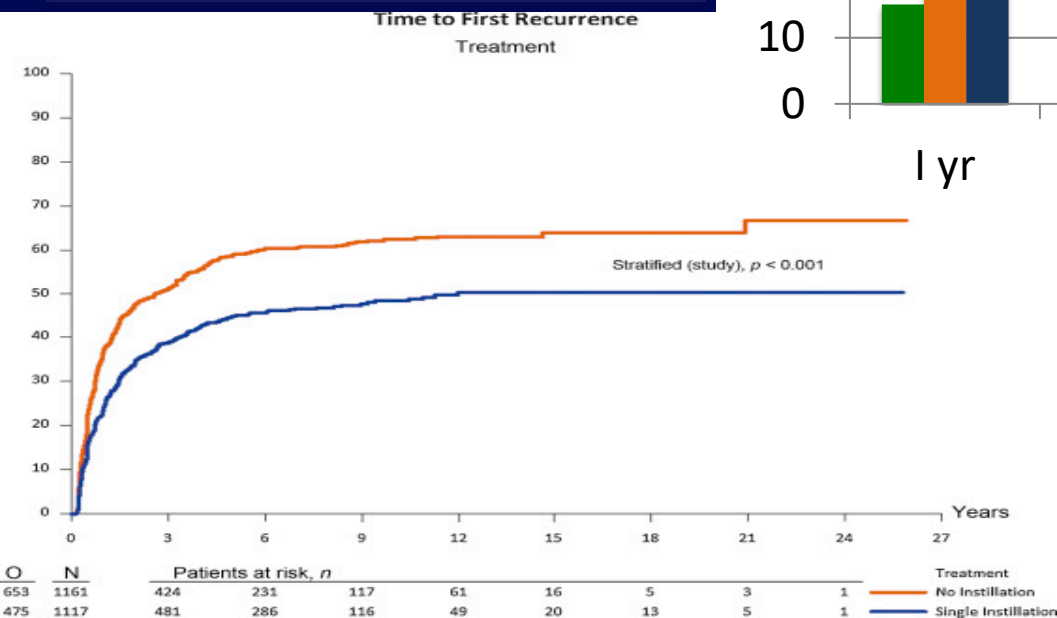
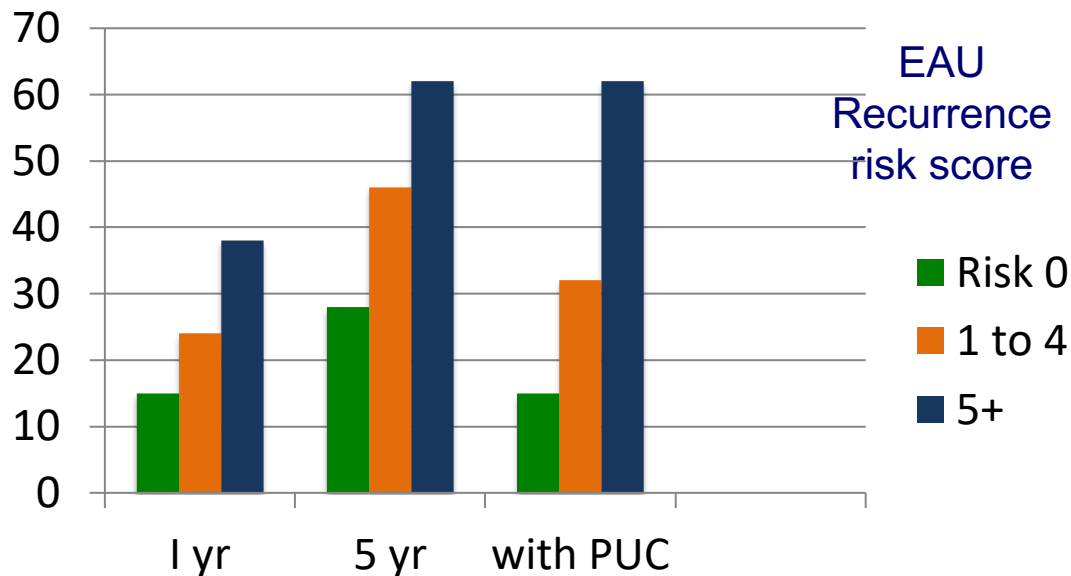
Controversies

- **High grade disease**
 - Re-TUR for HGTa when muscle present
 - Is Cystectomy still gold standard treatment for BCG non-responsive disease?
- **HGT1 Management**
 - If having cystectomy is re-TUR necessary
 - Immediate cystectomy vs. intravesical treatment

2016 Meta-analysis of 13 studies, 7 with individual patient data

n= 2278

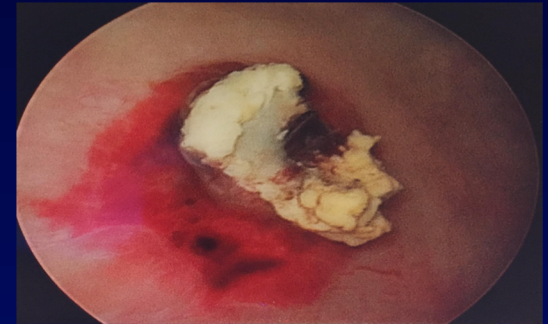
Low and intermediate risk
Decreases recurrence by 35%
(59% to 45% at 5 years)



Sylvester et al, Eur Urol 2016 69(2):231

Severe complications from post-TUR MMC

- MMC blocks healing
 - Calcifications
 - Ulcers
 - Pain, frequency, urgency
- Acute peritonitis
- Occasional 'bladder cripple' even from single dose

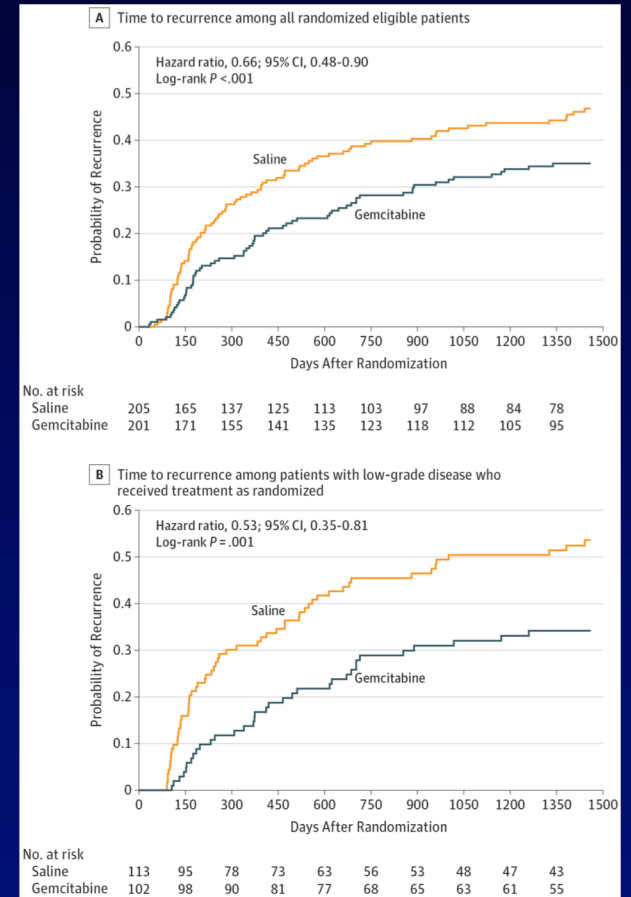


Slide courtesy of Dr. Eila Skinner

Post TUR gemcitabine - SWOG S0337

- 406 eligible patients
 - 37% recurrent tumors,
 - 68% solitary tumors
- Randomized to post-TUR gemcitabine vs saline
- Intent to treat: HR 0.66 recurrence at 4 yrs
- G3 toxicity 2.4% gemcitabine, 3.5% saline

Messing, EM. JAMA 2018; 319(18):1880.



Histopathology

- Variant cell types and growth patterns
 - Squamous cell differentiation
 - Glandular differentiation
 - Small cell (neuroendocrine)
 - Signet cell
 - Sarcoma
 - Plasmacytoid cell
 - Micropapillary
 - Nested

AUA Guidelines - Variant Histology

Due to the high rate of upstaging associated with variant histology, a clinician should **consider offering initial radical cystectomy** (Expert Opinion)

There is a lack of evidence regarding the efficacy of intravesical therapy for patient with non-muscle invasive urothelial carcinoma with variant histology.

Prognosis

- 10-Year Cancer Specific Survival
 - 70-85% high-grade
 - >95% in low-grade
- Risk stratification in NMIBC important for management

| | Risk of Progression (%) | Risk of Recurrence (%) |
|---------------|-------------------------|------------------------|
| Low-Grade Ta | 6 | 55 |
| High-Grade T1 | 17 | 45 |

Palou J, et al. *Eur Urol.* 2012;62:118-25; Cookson MS, et al. *J Urol.* 1997;158:62-67; Leblanc B, et al. *J Urol.* 1999;162:1946-1950.

Determining the Role of Cystectomy for High-grade T1 Urothelial Carcinoma

Siamak Daneshmand, MD

Clinics Review Articles

UROLOGIC CLINICS OF NORTH AMERICA

**Diagnosis, Evaluation,
and Treatment of
Non-Muscle Invasive
Bladder Cancer**

EDITOR

Sam S. Chang

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Samir S. Taneja

- Interpretation of lamina propria invasion may be very difficult in TUR specimens, especially when there is a high degree of cautery artifact.
- Up to 40% of patients with high grade clinical T1 or Tis disease are upstaged on the final pathology at the **time of cystectomy**

High Grade T1 Bladder Cancer Problems:

- Not all high grade T1 tumors are really T1
 - Up to 25% have muscle invasion on re-TUR
- There are no randomized trials comparing intravesical therapy to cystectomy for high grade bladder cancer
- 30% of patients initially treated with intravesical therapy will ultimately fail and require cystectomy
- Up to 30% of patients with high grade T1 disease on presentation will ultimately die of their disease

Early Versus Deferred Cystectomy for Initial High-Risk pT1G3 Urothelial Carcinoma of the Bladder: Do Risk Factors Define Feasibility of Bladder-Sparing Approach?

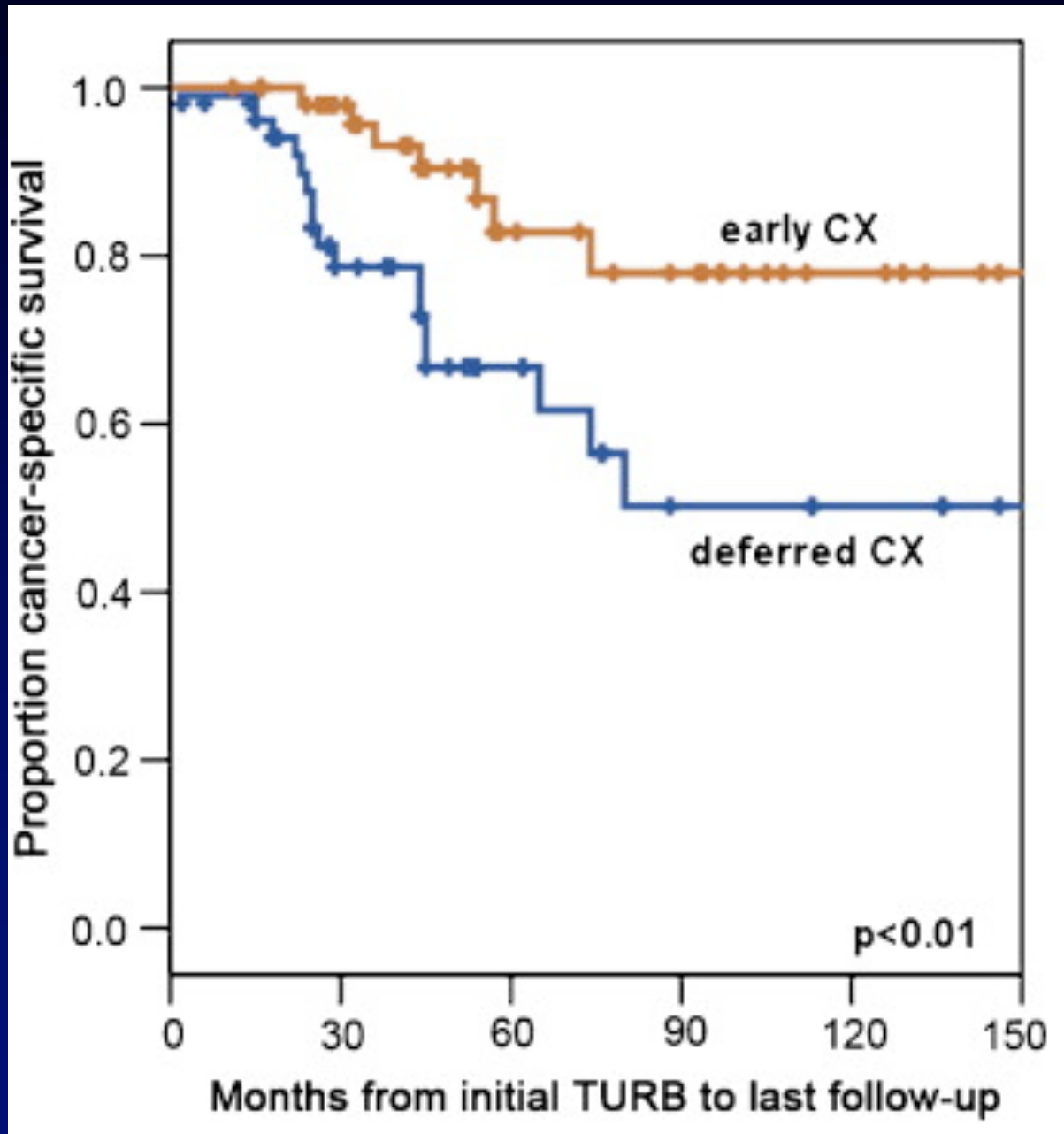
Stefan Denzinger*, Hans-Martin Fritsche, Wolfgang Otto, Andreas Blana, Wolf-Ferdinand Wieland, Maximilian Burger

Department of Urology, University of Regensburg, Regensburg, Germany



Characteristics of 105 patients after initial TURB undergoing early or deferred cystectomy

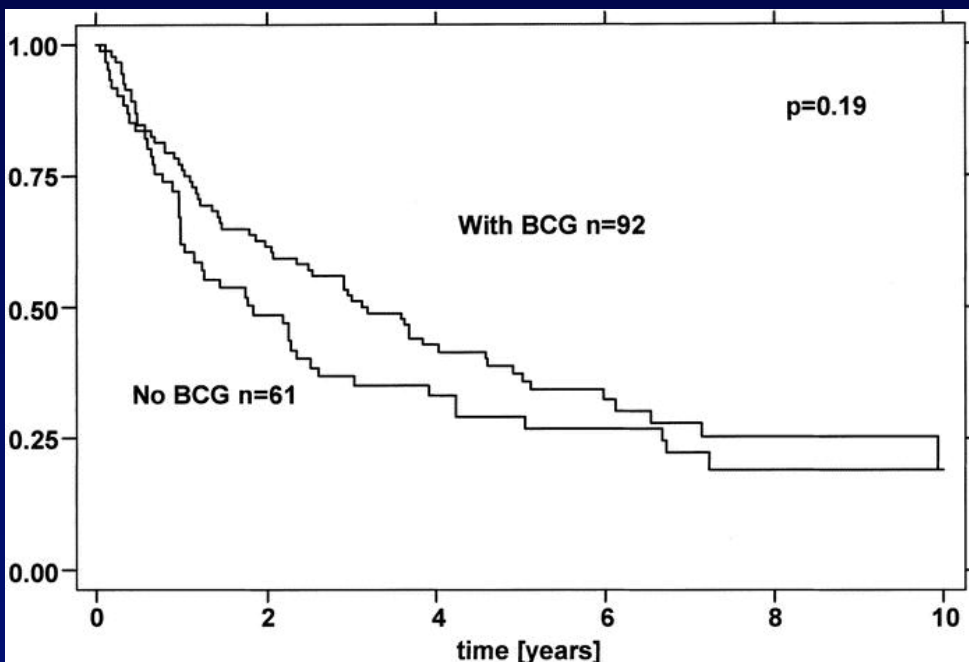
| | Early CX | Deferred CX | p value |
|------------------------------------|---------------------|---------------------|---------------|
| No. of patients | n = 54 | n = 51 | |
| No. of male patients | n = 32 | n = 30 | p = 0.72 (NS) |
| Median age (yr) | 73.5 (range, 36–86) | 75.2 (range, 43–84) | p = 0.21 (NS) |
| Multiple tumours n = 47/105 (45%) | n = 23 | n = 24 | p = 0.24 (NS) |
| Tumour size >3 cm n = 77/105 (73%) | n = 42 | n = 35 | p = 0.09 (NS) |
| CIS n = 48/105 (46%) | n = 21 | n = 27 | p = 0.18 (NS) |



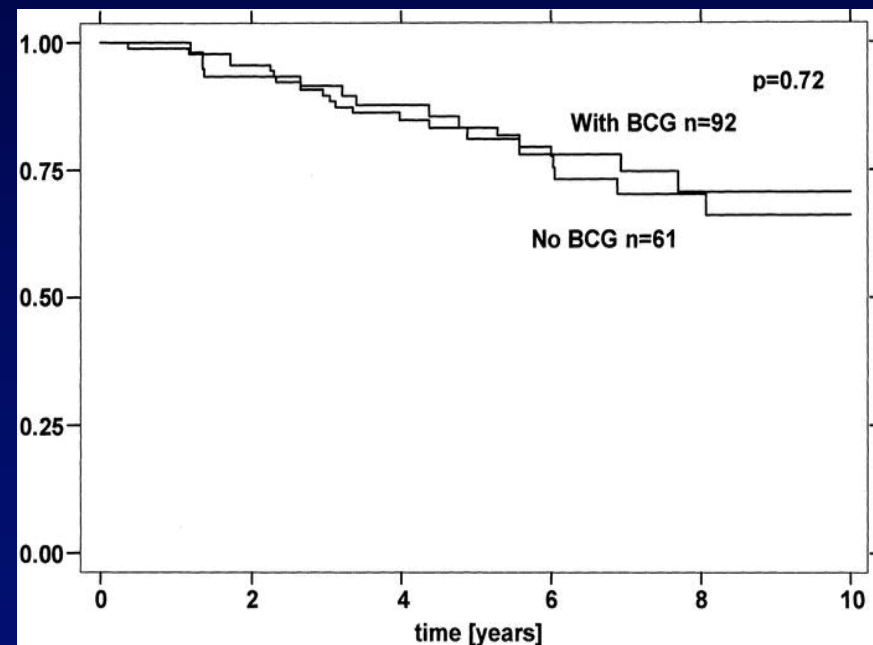
Would you take 50/50 chance?



BCG Delays Recurrence But May Not Impact Ultimate Cancer-Specific Survival



Recurrence-free survival



Cancer-specific survival

Review – Bladder Cancer

Long-term Cancer-specific Survival in Patients with High-risk, Non-muscle-invasive Bladder Cancer and Tumour Progression: A Systematic Review

Sven van den Bosch, J. Alfred Witjes *



Table 1 – Included trials having a prospective design

| Source | No. of patients | Median follow-up | Progression to MIBC, no. (%) | Death from disease, no. (%) | CSS in case of progression, % |
|--------------------------------|-----------------|---------------------|------------------------------|-----------------------------|-------------------------------|
| Di Stasi et al, 2006 [30] | 212 | 88 (IQR: 63–110) | 33 (16) | 23 (11) | 30 |
| Dalbagni et al, 2007 [31] | 89 | 52 (range: 16–90) | 22 (25) | 15 (17) | 32 |
| Gradmark et al, 2007 [36] | 250 | 123 (range: 46–176) | 58 (23) | 45 (18) | 22 |
| Esuvaranathan et al, 2007 [37] | 80 | 54 (range: 6–114) | 6 (8) | 5 (6) | 17 |
| Gofrit et al, 2009 [38] | 104 | 75 | 22 (21) | 12 (12) | 45 |
| Zieger et al, 2009 [39] | 125 | 80 (range: 6–142) | 67 (54) | 58 (46) | 13 |
| Sylvester et al, 2010 [5] | 323 | 110 | 50 (15) | 18 (6) | 64 |
| Totals | 1183 | 52–123 | 258 (22) | 176 (15) | 32 (range: 13–64) |

Decision Factors for High-Grade T1

- Associated CIS
- Deep lamina propria invasion (T1b)
- Significant voiding symptoms
- Lymphovascular invasion (LVI)
- Large or multifocal lesions
- Persistent T1G3 disease at 3 months following BCG therapy



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

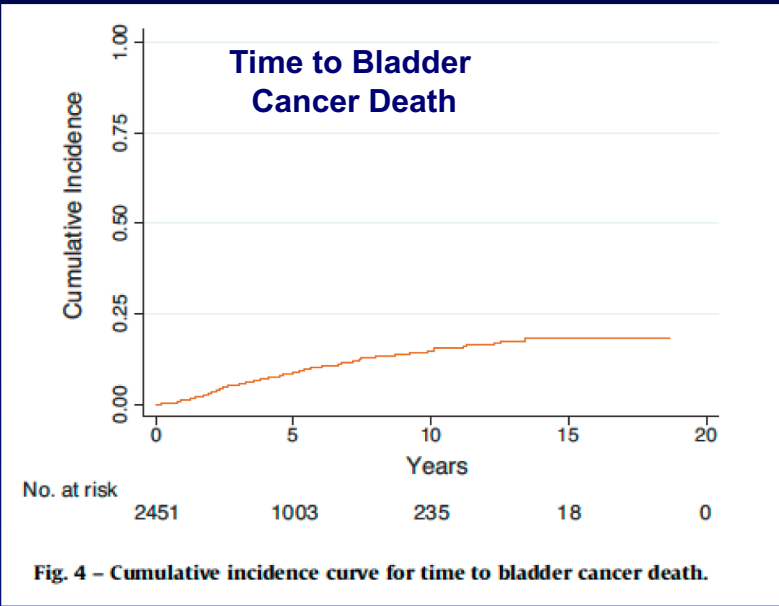
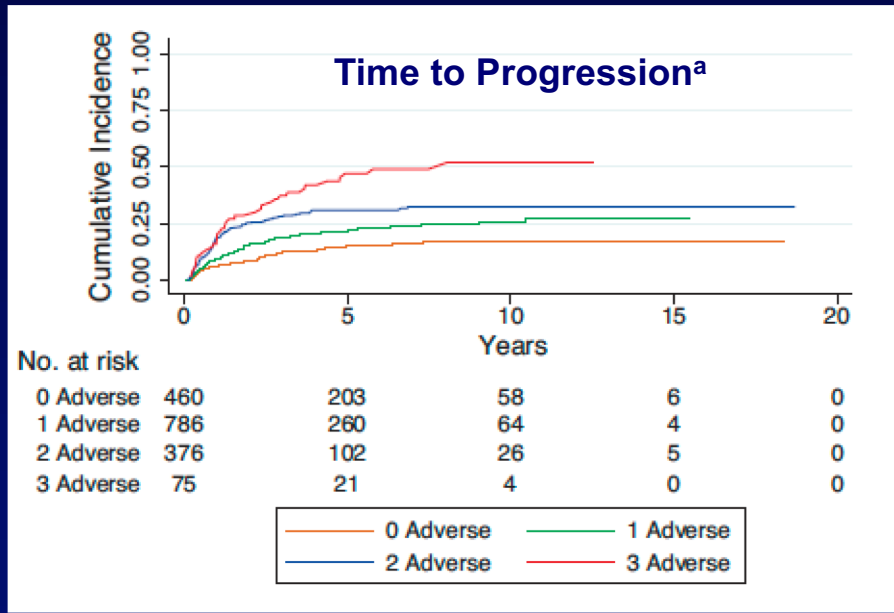


Fig. 4 – Cumulative incidence curve for time to bladder cancer death.



^aCumulative incidence curves for time to progression according to the number adverse prognostic factors for progression among patients ≥ 70 years, tumor size ≥ 3 cm, and presence of carcinoma in situ. Gontero P, et al. *Eur Urol.* 2015;67:74-82.

High-Risk Non-Invasive Disease: Advantages of Early Cystectomy

- Obtain accurate pathologic staging
- More appropriate for nerve-sparing approach
- Avoids multiple intravesical treatments
- Better cure rate

Node Positivity in T1

| Author | N | Positive Nodes |
|-----------------|-----------------------|----------------|
| Daneshmand 2018 | 603 cT1 | 12% |
| | 211 cT1 (with muscle) | 7% |
| Thalman 2004 | 29 | 14% |
| Weisner 2005 | 188 | 16% |
| Huguet 2005 | 31 | 10% |

Daneshmand S. *Urol Clin North Am.* 2013;40:233-247.

Molecular prognostication?

CLINICAL
Genitourinary
Cancer
Prostate, Kidney, & Bladder

Molecular Progression Risk Score for Prediction of Muscle Invasion in Primary T1 High-Grade Bladder Cancer

Ho Won Kang, Sung Pil Seo, Yeon Gwan Kim, Xuan-Mei Piao, Ye-Hwan Kim, Il-Ho Park, Sok Ha, Won Tae Kim, Yong-Ju Lee, Cheol Lee, Sung-Kwon Moon, Yong-Ho Kim, Seok-Joong Yun✉, Wun-Jae Lee
Published Online: February 23, 2017




Altered expression of HER-2 and the mismatch repair genes MLH1 and MSH2

Translational **Oncology**

www.transonc.com

Volume 10 Number xx Month 2017 pp. 340–345 **340**

High Androgen Receptor mRNA Expression Is Independently Associated with Prolonged Cancer-Specific and Recurrence-Free Survival in Stage T1 Bladder Cancer 

Danijel Sikic^{*,1}, **Johannes Breyer^{†,1}**, **Arndt Hartmann^{‡,1}**, **Maximilian Burger^{†,1}**, **Philipp Erben^{§,1}**, **Stefan Denzinger[†]**, **Markus Eckstein^{‡,1}**, **Robert Stöhr^{‡,1}**, **Sven Wach^{*,1}**, **Bernd Wullich^{*,1}**, **Bastian Keck^{*,1}**, **Ralph M. Wirtz^{†,1}** and **Wolfgang Otto^{†,1}**

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Conclusions



- Patient selection is the key
- Repeat aggressive TUR is required before considering conservative management
- The longer you use *ineffective* intravesical therapies, the higher the chance of metastasis
- For healthy patients with **high-risk factors**, initial **cystectomy** should be recommended