

**13<sup>η</sup> Εβδομάδα Ειδικευομένων Ουρολόγων 2018**

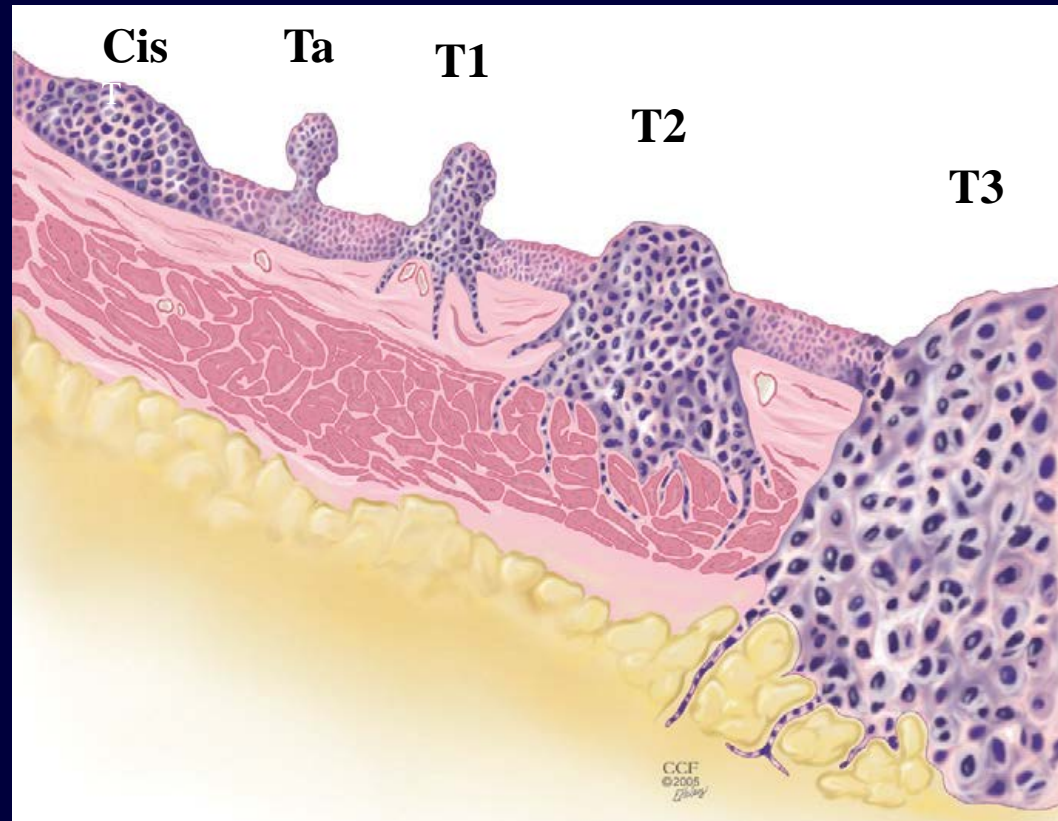
*Αντιμετώπιση μη Μυοδηθητικού Καρκίνου  
Κύστης Υψηλού Κινδύνου (T1G3)*

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Γ.Ν.Α. "Ο ΕΥΑΓΓΕΛΙΣΜΟΣ"**



# TCC : Συχνότητα κατά στάδιο

- Το 20-25 % των νεοδιαγνωσθέντων Ca κύστης είναι μυοδηθητικά
- Το 75-85% των νεοδιαγνωσθέντων Ca είναι μη μυοδηθητικά  
Ta:70%, T1:20%,CIS:10%
- Το 15-30% των μη μυοδηθητικών, high grade όγκων εξελίσσονται σε μυοδηθητικά στην 5-ετία



# NMI Bladder Cancer

Recurrence  
(Υποτροπή)

Progression  
(Εξέλιξη)



Survival  
(Επιβίωση)

# WHO

## International Society of Urologic Pathology Consensus Classification

TUMOR TYPE	% RELATIVE FREQUENCY	% PROGRESSION	% DEATHS
<b>Noninvasive</b>			
Papilloma	10	0-1	0
Papillary urothelial neoplasm of low malignant potential	20	3	0-1
Papillary cancer low grade (TaG1)	20	5-10	1-5
Papillary cancer high grade (TaG3)	30	15-40	10-25
<b>Invasive</b>			
Papillary cancer (T1G3)	20	30-50	33
<b>Carcinoma in Situ</b>			
Primary	10	>50	—
Secondary	90		

From Donat SM. Evaluation and follow-up strategies for superficial bladder cancer. Urol Clin North Am 2003;30:765-6.



MANAGEMENT OF STAGE T1 TUMORS OF THE BLADDER:  
INTERNATIONAL CONSENSUS PANEL

ALAN M. NIEDER, MAURIZIO BRAUSI, DONALD LAMM, MICHAEL O'DONNELL,  
KYOUICHI TOMITA, HENRY WOO, AND MICHAEL A. S. JEWETT

**TABLE III. Progression in T1G3 urothelial carcinoma of the bladder without the use of bacille Calmette-Guérin**

Study	N	Progression (%)	Follow-up (mo)
Heney <i>et al.</i> (1983)	27	48	36
RUTT (1985)	430	31	60
Malmstrom (1987)	7	43	60
Jakse (1987)	31	33	60
Kaubisch (1991)	18	50	36
Mulders (1994)	48	27	48
Klan (1995)	17	65	72
Holmang (1997)	58	48	84
Total	519	33	—

## T1 G3 at 5yrs

- **Recurrence : 80%**
- **Progression : 30-50%**

# 1973 WHO vs.1998 WHO/ISUP

## WHO 1973

Papilloma

Grade I

Grade II

**Grade III**

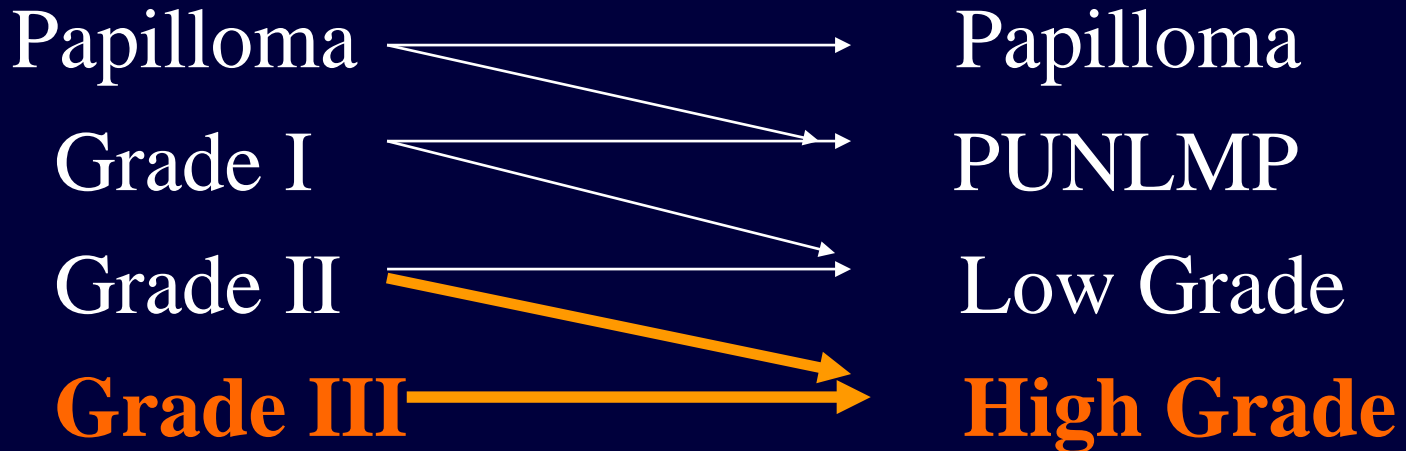
## WHO 1998

Papilloma

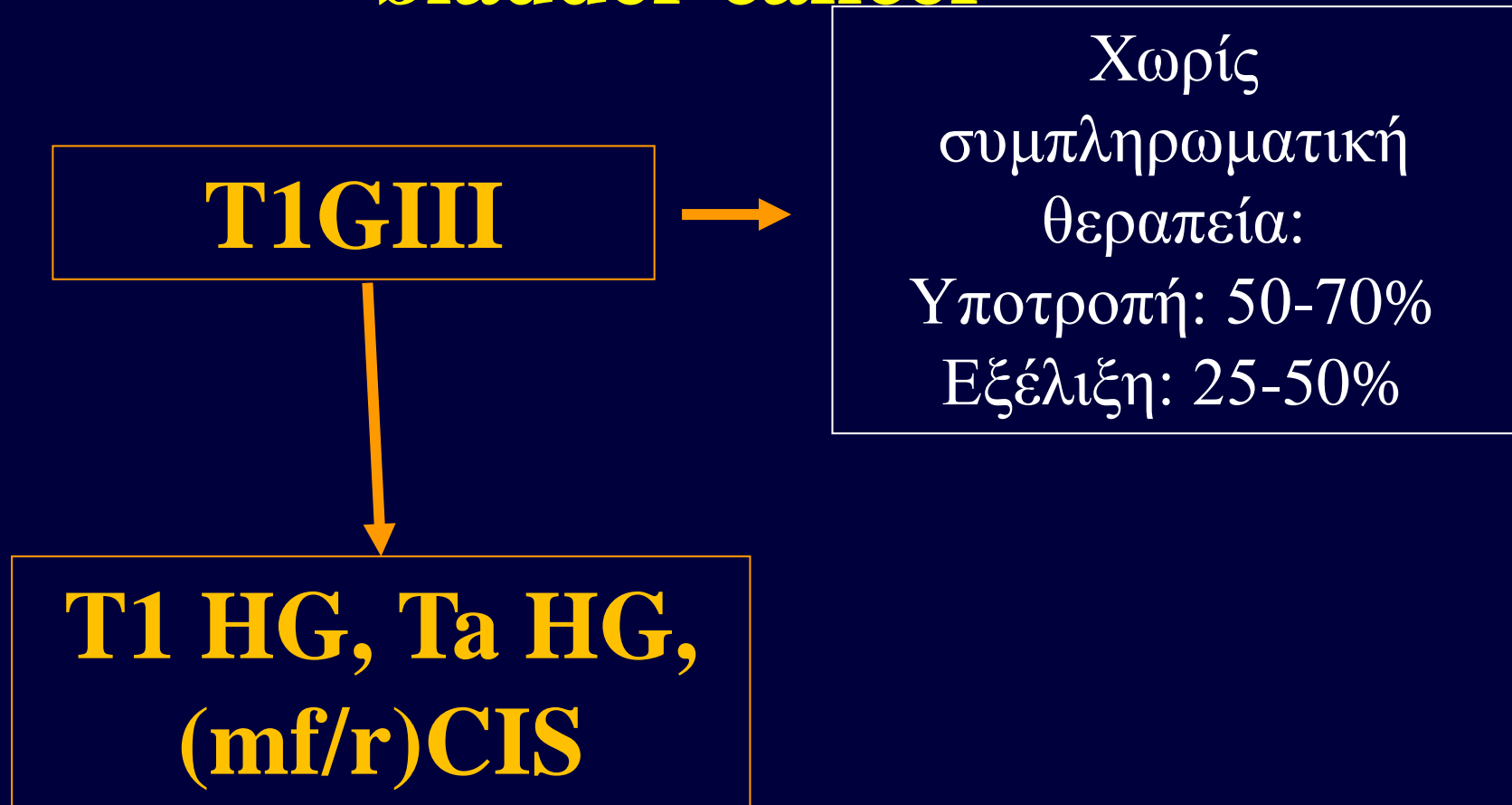
PUNLMP

Low Grade

**High Grade**



# High Risk non muscle invasive bladder cancer



# High Risk non muscle invasive bladder cancer

Low-risk tumours	Primary, solitary, Ta, G1 (low grade), < 3 cm, no CIS
Intermediate-risk tumours	All tumours not defined in the two adjacent categories (between the category of low and high risk)
High-risk tumours	Any of the following: <ul style="list-style-type: none"><li>• T1 tumour</li><li>• G3 (high grade) tumour</li><li>• CIS</li><li>• Multiple and recurrent and large (&gt; 3 cm) Ta G1G2 tumours (all conditions must be presented in this point)</li></ul>



# Πρόγνωση μη Μυοδηθητικού Καρκίνου Κύστης

Factor	Recurrence	Progression
Number of tumors		
Single	0	0
2 to 7	3	3
≥8	6	3
Tumor size		
<3 cm	0	0
≥3 cm	3	3
Prior recurrence rate		
Primary	0	0
≤1 rec/yr	2	2
>1 rec/yr	4	2
T category		
Ta	0	0
T1	1	4
CIS		
No	0	0
Yes	1	6
Grade		
G1	0	0
G2	1	0
G3	2	5
Total score	0-17	0-23

Recurrence score	Prob recurrence 1 year (95% CI)	Prob recurrence 5 years (95% CI)
0 <b>Low</b>	15% (10%, 19%)	31% (24%, 37%)
1-4 <b>Interm.</b>	24% (21%, 26%)	46% (42%, 49%)
5-9 <b>Interm.</b>	38% (35%, 41%)	62% (58%, 65%)
10-17 <b>High</b>	61% (55%, 67%)	78% (73%, 84%)
Progression score	Prob progression 1 year (95% CI)	Prob progression 5 years (95% CI)
0 <b>Low</b>	0.2% (0%, 0.7%)	0.8% (0%, 1.7%)
2-6 <b>Interm.</b>	1.0% (.4%, 1.6%)	6% (5%, 8%)
7-13 <b>Interm.</b>	5% (4%, 7%)	17% (14%, 20%)
14-23 <b>High</b>	17% (10%, 24%)	45% (35%, 55%)

# Αντιμετώπιση T1GIII



- TUR BT
- Άμεση μτ/κή ενδοκυστική έγχυση χημειοθεραπευτικού (Grade A Rec.) ??
- Re-TUR BT ??

# Αρχική TUR



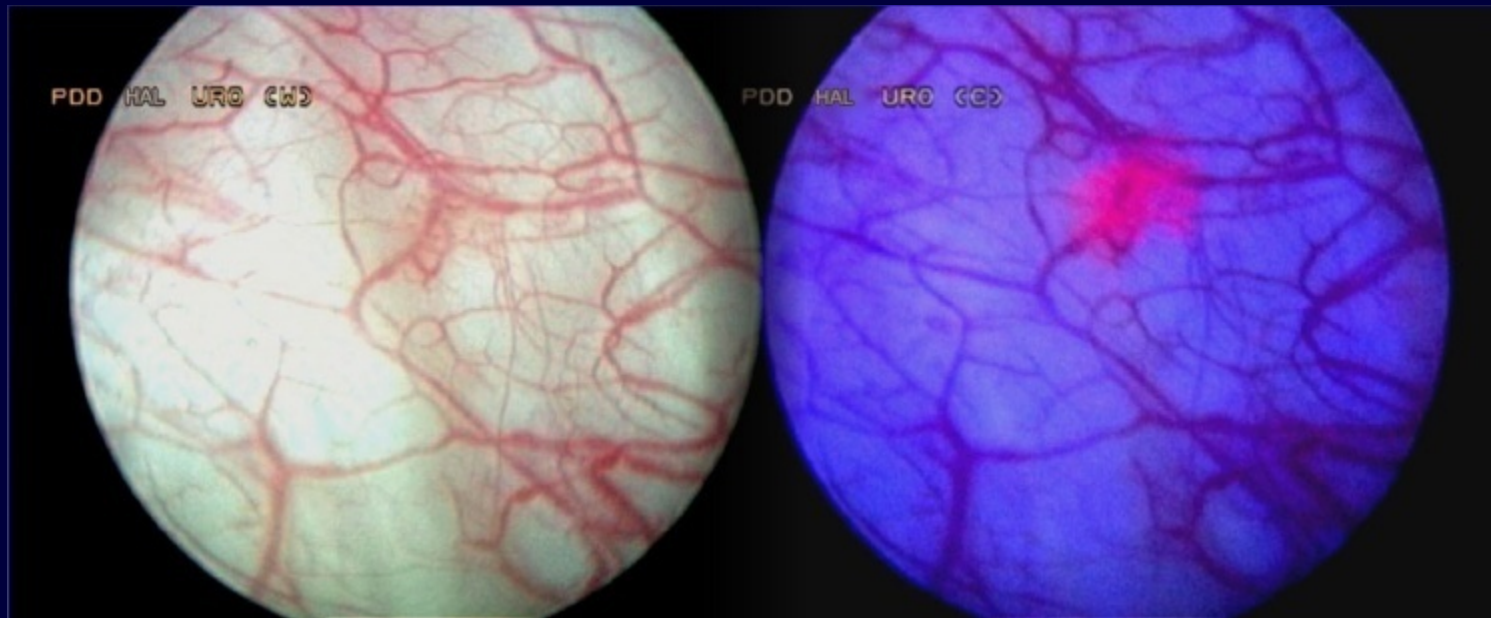
«Ιδανική»TUR σε τρία παρασκευάσματα:

- Εξωφυτικός όγκος
- Βάση όγκου + μυικός χιτώνας
- Όρια όγκου

Βιοψίες μόνο από παθολογικό βλεννογόνο (CIS)  
Τυχαίες βιοψίες σε θετική κυτταρολογική χωρίς εμφανή  
όγκο ή σε συμπαγή μη θηλωματώδη όγκο

# Optimizing TUR BT Φωτοδυναμική Διάγνωση (PDD)

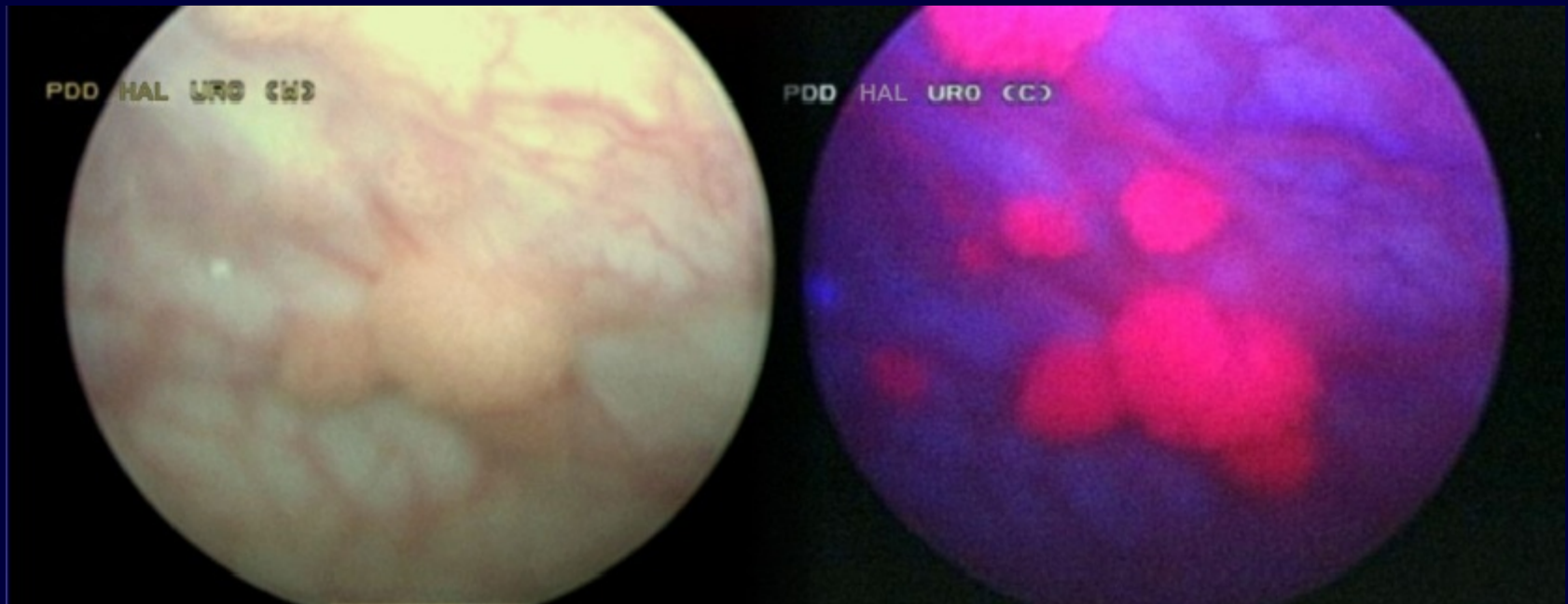
Small Papillary Tumor



Zaak, Munik 2002

# Optimizing TUR BT Φωτοδυναμική Διάγνωση (PDD)

Larger multifocal papillary tumors

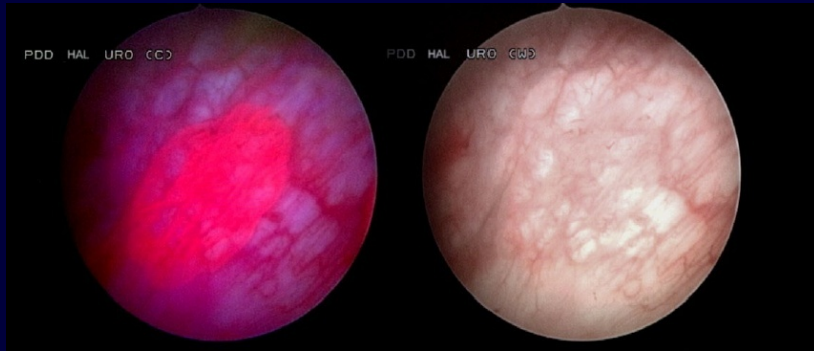


Zaak, Munik 2002

# Optimizing TUR BT

## Φωτοδυναμική Διάγνωση (PDD)

### Histologically confirmed CIS



- CIS είναι ένας επίπεδος , high-grade, μη-μυοδηθητικός ουροθηλιακός καρκίνος .
- Επισκοπικά: δ.δ. φλεγμονή
- Μπορεί να είναι πολυεστιακό και να εντοπίζεται στην ανώτερη αποχετευτική μοίρα, στη προστατική ουρήθρα ή στους προστατικούς πόρους.

### Κλινικοί τύποι CIS:

- Πρωτοπαθές
- Δευτεροπαθές
- Σύγχρονο με θηλωματώδες TCC
- Υποτροπιάζον μετά από ενδοκυστική θεραπεία

Χωρίς θεραπεία :

54% εξελίσσεται σε μυοδηθητικό CA

# Φωτοδυναμική Διάγνωση (PDD)

- Η PDD μειώνει τις υποτροπές στα μη μυοδηθητικά TCCs κατά 9% στους πρώτους 9 μήνες μετά την TUR.

Stenzl A, et al. J Urol 2010 Nov;184(5):1907-13

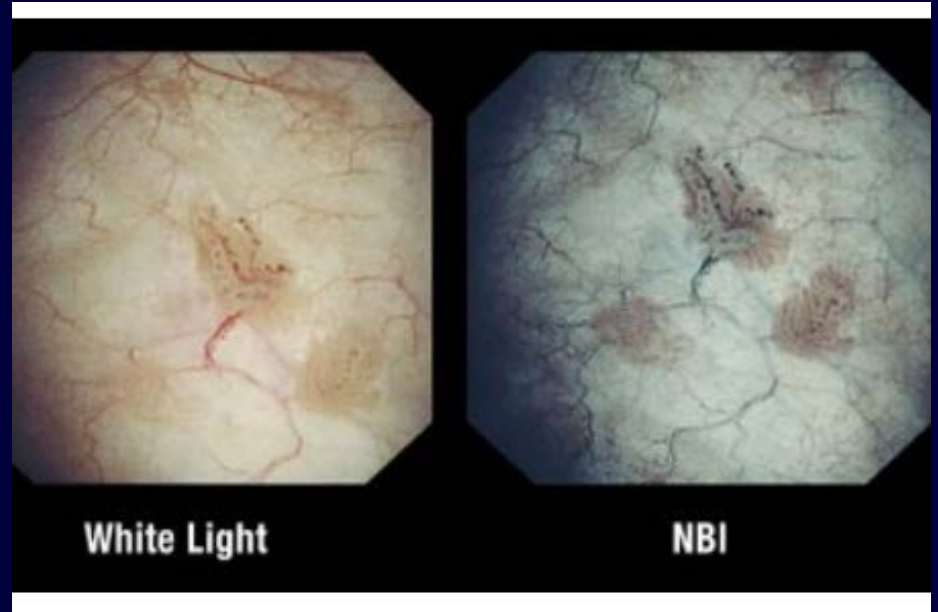
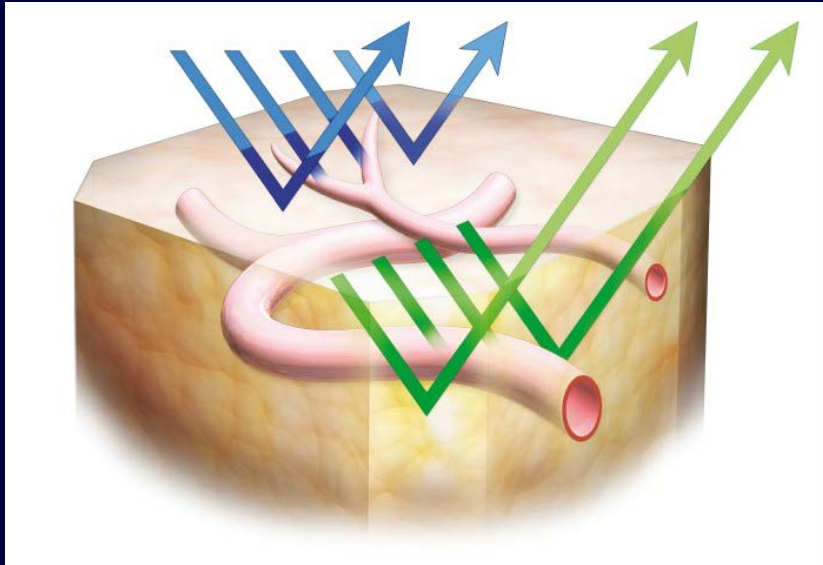
- Μέχρι στιγμής δεν έχει φανεί όφελος στη πρόληψη της εξέλιξης ή στη βελτίωση της επιβίωσης

If equipment is available, fluorescence-guided (PDD) biopsy should be performed instead of random biopsies when bladder CIS or high-grade tumour is suspected (e.g., positive cytology, recurrent tumour with previous history of a high-grade lesion).

B



# NBI



Narrow-band imaging is an imaging technique for endoscopic medical tests, where light of specific blue and green wavelengths is used to enhance the detail of certain aspects of the surface of the mucosa



# Άμεση μετ/κή ένδοκυστική ΧΜΘ



- Επαρκής θεραπεία μόνο για τα low risk ( EORTC score :0-2)
- Ανεπαρκής για όλα τα υπόλοιπα (EORTC score >3)
- Υποστηρίζεται ισχυρά να γίνεται σε όλα τα NMIBC

# Άμεση μετ/κή ένδοκυστική ΧΜΘ σε high risk TCC



- Δεν υπάρχουν μέχρι στιγμής δεδομένα που να αποδεικνύουν οποιοδήποτε ρόλο της άμεσης έγχυσης ΧΜΘ σε high risk όγκους προ θεραπείας με BCG
- ΠΡΟΣΟΧΗ στην εξαγγείωση του ΧΜΘ

# **Systematic Review and Individual Patient Data Meta-analysis of Randomized Trials Comparing a Single Immediate Instillation of Chemotherapy After Transurethral Resection with Transurethral Resection Alone in Patients with Stage pTa–pT1 Urothelial Carcinoma of the Bladder: Which Patients Benefit from the Instillation?**

*Richard J. Sylvester<sup>a,\*</sup>, Willem Oosterlinck<sup>b</sup>, Sten Holmang<sup>c</sup>, Matthew R. Sydes<sup>d</sup>, Alison Birtle<sup>e</sup>, Sigurdur Gudjonsson<sup>f</sup>, Cosimo De Nunzio<sup>g</sup>, Kikuo Okamura<sup>h</sup>, Eero Kaasinen<sup>i</sup>, Eduardo Solsona<sup>j</sup>, Bedeir Ali-El-Dein<sup>k</sup>, Can Ali Tatar<sup>l</sup>, Brant A. Inman<sup>m</sup>, James N'Dow<sup>n</sup>, Jorg R. Oddens<sup>o</sup>, Marek Babjuk<sup>p</sup>*

# Systematic Review and Individual Patient Data Meta-analysis of Randomized Trials Comparing a Single Immediate Instillation of Chemotherapy After Transurethral Resection with Transurethral Resection Alone in Patients with Stage pTa–pT1 Urothelial Carcinoma of the Bladder: Which Patients Benefit from the Instillation?

EUROPEAN UROLOGY 69 (2016) 231–244

In summary, although a single immediate instillation of chemotherapy reduced the relative risk of recurrence by 35% and the 5-yr recurrence rate by 14%, it is not effective in patients with a prior recurrence rate of more than one recurrence per year or in patients with EORTC recurrence risk score  $\geq 5$ . It does not prolong either the time to progression or the time to death due to BCa. Exploratory

# Re-TUR BT

Herr (1999)

- 96 pts with initial TUR  $\leq$  T2
- Re TUR within 2-6 weeks
- Only 24% were free of Tumor with 1<sup>st</sup> TUR

T1 pts

- 78% had residual tumor
- 28% found to have T2 disease

Herr HW. J Urol 1999;162:74-76

# Γιατί χρειάζεται η Re-TUR BT?

- Υπερσταδιοποίηση (pT2) σε 2-30%  
αρχική TUR με μυϊκό χιτώνα 15%  
χωρίς μυϊκό χιτώνα 45%
- Υπολοιπόμενος όγκος κατά την Re-TUR  
σε T1: 33-53%

Bas W.G. van Rhijn et al. Eur Urol. 56;430,2009

EAU Guidelines 2010

## Γιατί χρειάζεται η Re-TUR BT?

- Η πρόγνωση των ασθενών με pT1 εξαρτάται από την ιστολογική της Re-TUR
- Εξέλιξη σε pT2 όγκο 5 έτη μετά την TUR:  
Re-TUR: pT1, 75 /92 pts (82%)  
Re-TUR : pT0/Ta, 49/ 260 pts (19%)

Herr HW, et al.. Can restaging transurethral resection of T1 bladder cancer select patients for immediate cystectomy? J Urol 2007;177:75–9.

# Γιατί χρειάζεται η Re-TUR BT?

- Η ανταπόκριση στην ενδοκυστική θεραπεία (BCG , MMC) είναι καλύτερη μετά από Re-TUR

Herr HW. J Urol 2005;174:2134–7

Divrik RT, et al. J Urol 2006;175:1641–4

- Η ύπαρξη τυχόν υπολειπόμενου όγκου μετά την αρχική TUR σε ασθενή που υποβάλλεται σε BCG θεραπεία θα εμφανισθεί κατά το fu στο 1<sup>ο</sup> τρίμηνο και θα χαρακτηριστεί ως BCG refractory όγκος με εντελώς διαφορετική προγνωστική σημασία

Ιδία παρατήρηση



# Re-TUR BT

A second TURB is recommended in the following situations:	A
<ul style="list-style-type: none"><li>- after incomplete initial TURB;</li><li>- if there is no muscle in the specimen after initial resection, with exception of Ta G1 tumours and primary CIS;</li><li>- in all T1 tumours;</li><li>- in all G3 tumours, <b>except primary CIS.</b></li></ul>	
A second TURB should be performed 2-6 weeks after initial resection.	C

**Τυχαίες Bx/ Bx προστατικής ουρήθρας:**

**Σε περίπτωση ύποπτου βλενογόννου, όγκου στον αυχένα της  
κύστης ή υποψία CIS**

**Μπορεί να γίνει κατά τη Re-TUR**

**Απόλυτη ένδειξη στο T1GIII**

# En bloc resection: challenges

- Large specimen retrieval (Carpet technique?)
- Localisation: bladder neck, dome (no realistic flexible scenario up to now!)

**Table 2.** Exit strategies for tumor retrieval

	Author
Trapping and evacuation in extraction bags	Fritsche et al., 2011 [37]
Vaporization to reduce size of the specimen and extraction of the base only	Geavlete et al., 2012 [42]
Morcellation after securing the right resection level by 'antegrade' resection	Sureka et al., 2014 [46]
Ellick evacuator or nephroscopy sheet and laparoscopic grasper for larger tumors	Hurle et al., 2016 [21]

cTURB, conventional TURBT; ERBT, en bloc resection of bladder tumors; FU, follow-up, n.a. not applicable, \*RCT from previous review period, recurrence and ERBT.

Herrmann TR et al. Curr Opin Urol 2017

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# Expectations

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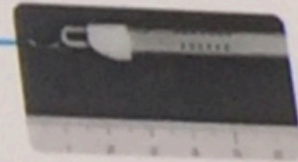
- Respect of oncologic principals
- Improvement of staging and grading
- Reduction of spilling and seeding
- Avoiding of re-do procedures
- Short learning curve
- Economic

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# En bloc resection: history

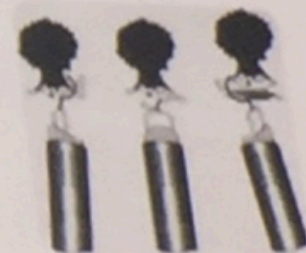
## Principle of en bloc „J-Electrode“

Kawada T et al. J Urol 1997; 157(6):2225 – 2226



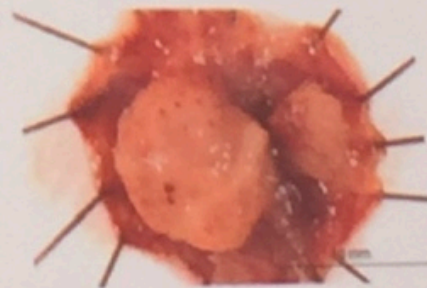
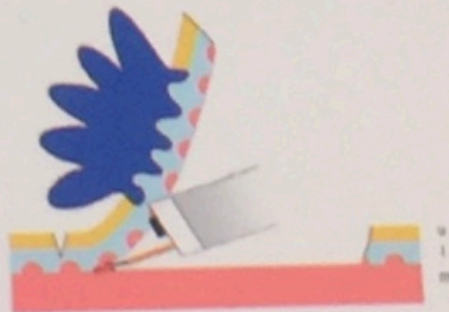
## Laser Resektion

Das A, Gilling P, Fraundorfer M (1998). Tech Urol 4(1):12-14



## Transurethral resection of superficial bladder tumor in 1 piece (TURBO) Ho:YAG

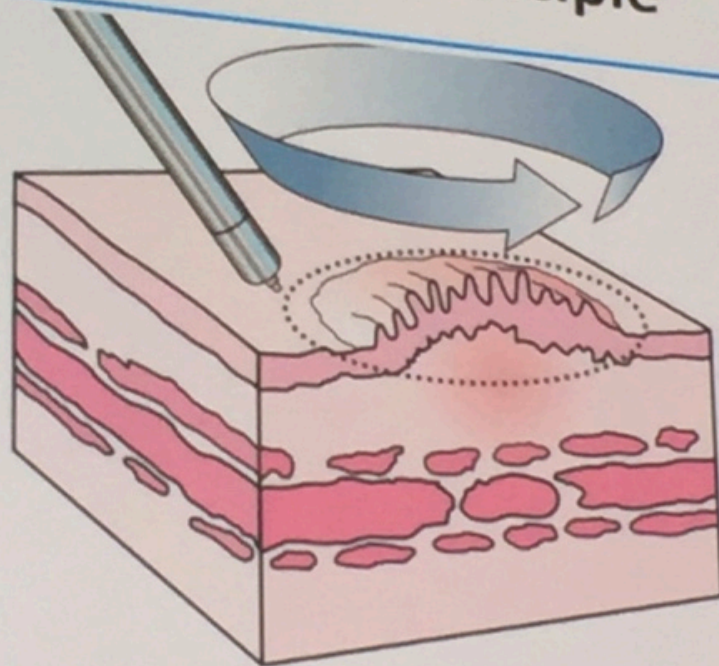
Ukai et al. J Urol 2000; Urol 163(3):878-879.



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# En bloc resection: principle



Current evidence for transurethral en bloc resection of non-muscle-invasive bladder cancer

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THEOBALT BACH<sup>1</sup>, ANDREAS J. GROSS<sup>1</sup>, UDO NAGELE<sup>1</sup>, PIERRE CONORT<sup>1</sup>,  
AXEL S. MERSEBURGER<sup>1</sup>, MARKUS A. KUCZYK<sup>1</sup>, THOMAS R. W. HERRMANN<sup>1</sup>

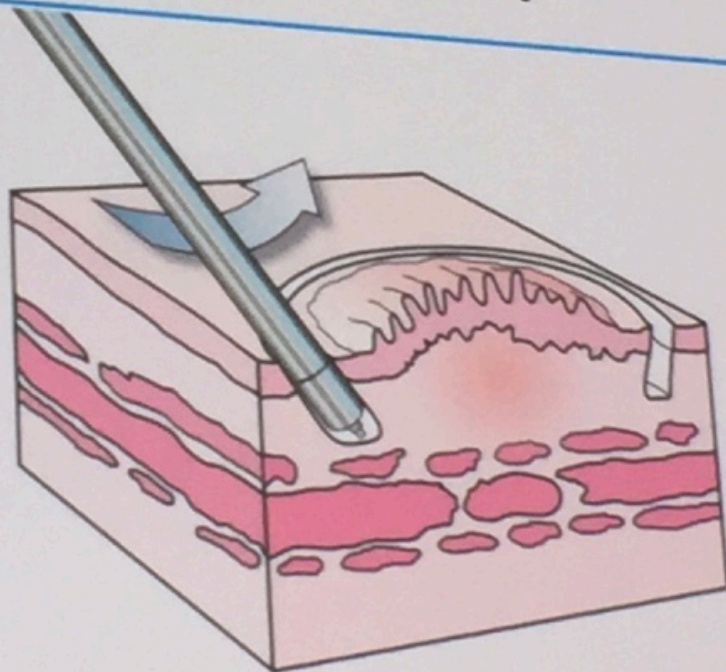
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Kramer M et al. Minim Invasive Ther Allied Technol. 2014 Aug;23(4):206-13.

Meeting of the EAU Section of Oncological Urology  
8 January 2018 Amsterdam, The Netherlands



# En bloc resection: principle



Current evidence for transurethral en bloc resection of non-muscle-invasive bladder cancer

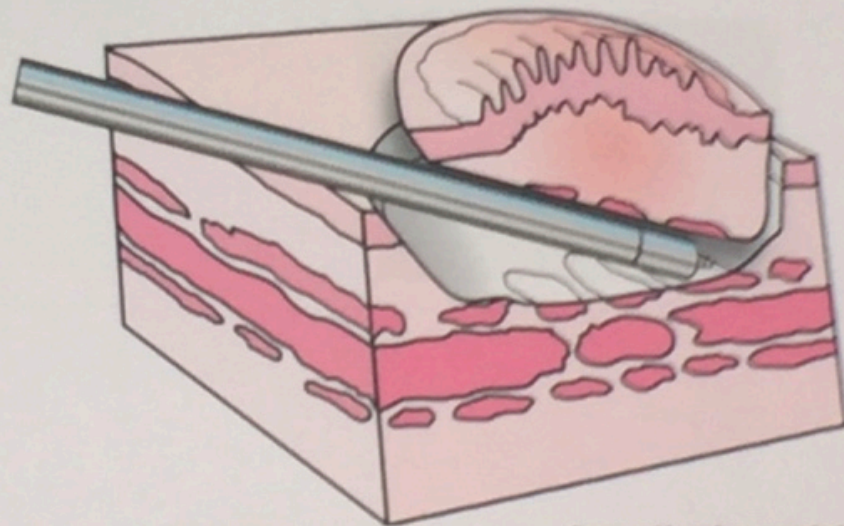
MARIO W. KRAMER<sup>1</sup>, ISLAM F. ABDULKAWI<sup>1,2</sup>, MATTHIAS WULTERS<sup>1</sup>,  
THORSTEN BACH<sup>1</sup>, ANDREAS J. GROB<sup>1</sup>, UDO NAGELS<sup>1</sup>, PIERRE CONORT<sup>1</sup>,  
AXEL S. MERSEBURGER<sup>1</sup>, MARKUS A. KUCZYK<sup>1</sup>, THOMAS R. W. HERGMANN<sup>1</sup>

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2014 Aug;23(4):206-13.

Kramer M et al. Minim Invasive Ther Allied Technol. 2014 Aug;23(4):206-13.

# En bloc resection: principle



Current evidence for transurethral en bloc resection of non-muscle-invasive bladder cancer

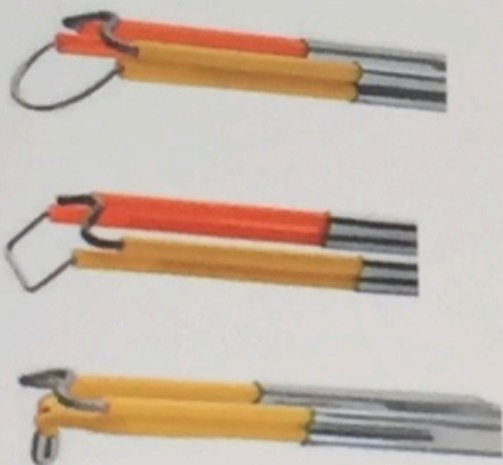
MARCO W. KRÄMER<sup>1</sup>, BEATRICE A. KRÄMER<sup>1</sup>, MATTHEW WOLTER<sup>2</sup>,  
THORSTEN BACH<sup>3</sup>, ANDREAS J. GROSS<sup>4</sup>, GÜNTER H. HERRLICH<sup>5</sup>, JOHANN LÖHNER<sup>6</sup>,  
AKSEL S. MERSEBURGER<sup>7</sup>, MARKUS A. RUCZYNSKI<sup>8</sup>, TORSTEN W. ZEIGER<sup>9</sup>

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Krämer M et al. Minim Invasive Ther Allied Technol. 2014 Aug; 23(4):206-13.



# En bloc resection: classic



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January 2018 Amsterdam, The Netherlands



# En bloc resection

Waterjet Hydrosurgery  
DOI: 10.1007/s00381-017-3603-8

ORIGINAL ARTICLE

Waterjet hydrodissection: first experiences and short-term outcomes of a novel approach to bladder tumor resection

U. Nagler, M. Kugler, A. Niklas, A. S. Merschinger,  
U. Watzke, G. Mikac, T. R. Herrmann



En Bloc

- Laser En Bloc
- Bipolar HF En Bloc
- Monopolar En Bloc

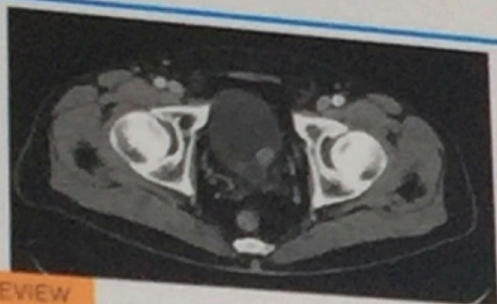


En Bloc *PLUS*

- HybridKnife®
- Needle injection

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# En bloc resection: Evidence = sparse



Current evidence for transurethral en bloc resection of non-muscle-invasive bladder cancer

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REVIEW



Transurethral en bloc resection of nonmuscle invasive bladder cancer: trend or hype

Thomas R.W. Herrmann<sup>1\*</sup>, Mathias Wolters<sup>1</sup>, and Mario W. Kramer<sup>1\*</sup>

available at [www.euroandrology.com](http://www.euroandrology.com)  
journal homepage: [www.euroandrology.com/abstracts](http://www.euroandrology.com/abstracts)

EAU

Review - Bladder Cancer

Current Evidence of Transurethral En-bloc Resection of Nonmuscle Invasive Bladder Cancer: Update 2016

Mario W. Kramer<sup>1</sup>, Vincenzo Altieri<sup>2</sup>, Rodolfo Harle<sup>3</sup>, Leifki Lazzaroli<sup>4</sup>, Axel S. Merseburger<sup>1</sup>, Jens Bannweiler<sup>5</sup>, Julian P. Struck<sup>6</sup>, Thomas R.W. Herrmann<sup>1\*</sup>

- (Laser) En bloc (EBRT) since 1997
- Data ERBT 27 publications
- 1 Meta-analysis EBRT
- >1300 patients
- LOE: non-analytic studies
- 2 RCTs

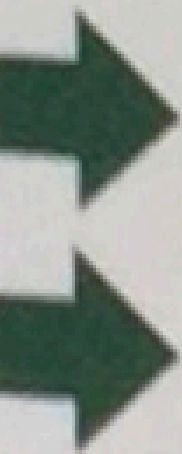
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## KEY POINTS

- ERBT is developing concept as an alternative to conventional TURBT.
- En bloc provides higher quality specimens with regard to LMP presentation and therefore analyzability and informative value.
- Today, roughly 60-70% seems to be suitable for ERBT, which mostly depends on tumor size and localization.
- Up to now, no significant advantage with regard to recurrence-free survival has been demonstrated.
- Although ERBT is 'on the market' for 18 years, data are still limited, but the recent publication supports the hypothesized potential.



# Πρόγνωση

EUROPEAN UROLOGY 49 (2006) 466-477

available at [www.sciencedirect.com](http://www.sciencedirect.com)  
journal homepage: [www.europeanurology.com](http://www.europeanurology.com)



European Association of Urology

## T1GIII ??

### Bladder Cancer

### Predicting Recurrence and Progression in Individual Patients with Stage Ta T1 Bladder Cancer Using EORTC Risk Tables: A Combined Analysis of 2596 Patients from Seven EORTC Trials

Richard J. Sylvester<sup>a,\*</sup>, Adrian P.M. van der Meijden<sup>b</sup>, Willem Oosterlinck<sup>c</sup>, J. Alfred Witjes<sup>d</sup>, Christian Bouffoux<sup>e</sup>, Louis Denis<sup>f,1</sup>, Donald W.W. Newling<sup>g,2</sup>, Karlheinz Kurth<sup>h,3</sup>

Factor	Recurrence	Progression
Number of tumors		
Single	0	0
2 to 7	3	3
≥8	6	3
Tumor size		
<3 cm	0	
≥3 cm	3	3
Prior recurrence rate		
Primary	0	0
≤1 rec/yr	2	2
>1 rec/yr		2
T category		
Ta	0	0
T1	1	4
CIS		
No	0	0
Yes	1	6
Grade		
G1	0	0
G2	1	0
G3	2	5
Total score	0-17	0-23

2596 pts in 7 EORTC trials, only 193 had T1GIII, no CIS, old intravesical chemo, no Re-TUR, no maintenance BCG

Recurrence score	Prob recurrence 1 year (95% CI)	Prob recurrence 5 years (95% CI)
0 <b>Low</b>	15% (10%, 19%)	31% (24%, 37%)
1-4 <b>Interm.</b>	24% (21%, 26%)	46% (42%, 49%)
5-9 <b>High</b>	38% (35%, 41%)	62% (58%, 65%)
10-17 <b>High</b>	61% (55%, 67%)	78% (73%, 84%)

Progression score	Prob progression 1 year (95% CI)	Prob progression 5 years (95% CI)
0 <b>Low</b>	0.2% (0%, 0.7%)	0.8% (0%, 1.7%)
2-6 <b>Interm.</b>	1.0% (.4%, 1.6%)	6% (5%, 8%)
7-13 <b>High</b>	5% (4%, 7%)	17% (14%, 20%)
14-23 <b>High</b>	17% (10%, 24%)	45% (35%, 55%)

# Πρόγνωση

**Table 3.** Factors by weight to calculate recurrence and progression scores using AIC to select most predictive model

Factor	Recurrence Score	Progression Score
Gender:		
M	0	0
F	3	0
Age:		
Less than 60	0	0
60–70	1	0
Greater than 70	2	2
Recurrent tumor:		
No	0	0
Yes	4	2
No. tumors:		
3 or Less	0	0
Greater than 3	2	1
T category:		
Ta	0	0
T1	0	2
Associated Tis:		
No	0	0
Yes	2	1
Grade:		
G1	0	0
G2	1	2
G3	3	6
Total scores	0–16	0–14

1062pts from CUETO trials, different scheme of BCG, 12 installation at 5-6 months, no post-operative chemo, no Re-TUR



## Bladder Cancer

### Prognostic Factors in Patients with Non-Muscle-Invasive Bladder Cancer Treated with Bacillus Calmette-Guérin: Multivariate Analysis of Data from Four Randomized CUETO Trials

### Predicting Nonmuscle Invasive Bladder Cancer Recurrence and Progression in Patients Treated With Bacillus Calmette-Guerin: The CUETO Scoring Model

Jesus Fernandez-Gomez,\* Rosario Madero, Eduardo Solsona, Miguel Unda, Luis Martinez-Piñeiro, Marcelino Gonzalez, Jose Portillo, Antonio Ojea, Carlos Pertusa, Jesus Rodriguez-Molina, Jose Emilio Camacho, Mariano Rabadan, Ander Astobieta, Manuel Montesinos, Santiago Isorna, Pedro Muntañola, Anabel Gimeno, Miguel Blas and Jose Antonio Martinez-Piñeiro

**J Urol. 182(5); 2195-2203, 2009**

**Table 4.** Recurrence and progression probabilities at 1, 2 and 5 years by total score

Score	% 1 Yr (95% CI)		% 2 Yrs (95% CI)		% 5 Yrs (95% CI)	
	Recurrence	Progression	Recurrence	Progression	Recurrence	Progression
0–4	8.24 (5.91–10.57)	1.17 (0.15–2.19)	12.6 (9.76–15.44)	2.16 (0.77–3.55)	20.98 (17.33–24.63)	3.76 (1.9–5.62)
5–6	12.07 (7.95–16.19)	3 (0.82–5.18)	22.28 (16.93–27.63)	4.97 (2.34–7.6)	35.57 (29.18–41.96)	11.69 (7.57–15.81)
7–9	25.36 (19.56–31.16)	5.55 (2.73–8.37)	39.61 (32.93–46.29)	11.95 (7.93–15.97)	47.65 (40.55–54.75)	21.26 (15.85–26.67)
10 or Greater	41.79 (28.05–55.53)	13.97 (6.64–21.3)	52.55 (38.48–66.62)	24.81 (15.6–34.02)	67.61 (53.67–81.55)	33.57 (23.06–44.08)

# T1 disease



Cat

or



Tiger?

Early recurrence,  
Grade,  
Multiplicity,  
Tumor extent and size,

Concomitant CIS,  
Urothelial carcinoma involving the prostatic mucosa or ducts,  
Depth of lamina propria invasion. (LOE 3)

*Cancer* 86: 1035–1043, 1999  
*J Urol* 163: 73–78, 2000.  
*J Urol* 164: 685–689, 2000.

## T1 Grade III



Cat

or



Tiger?

**BCG**

or

**Cystectomy**

*MANAGEMENT OF STAGE T1 TUMORS OF THE BLADDER:  
INTERNATIONAL CONSENSUS PANEL  
UROLOGY 66 (Suppl 6A): 108–125, 2005.*

# Molecular markers for predicting recurrence, progression and outcome

Brian Duggan et al. *Current Opinion in Urology* 2004, 14:277–286

- **Apoptosis/cell-cycle proteins: p53/retinoblastoma protein/Fas (n=15)**

P53, p73, pRb, p21, MDM2, Fas-Fas ligand system, p16INK4a & p14ARF, p16, p27, Bcl-2, Bax, Glusterin, Survivin, Chromosomal abnormalities, COX-2

- **Proliferative/mitogenic proteins (n=7)**

Mitotic activity index/mean area of 10 largest nuclei, Ki-67, HER-2/neu tyrosine kinase growth factor receptor, Vascular endothelial growth factor, Basic fibroblast growth factor, HB-EGF, FGFR3

- **Angiogenesis/cell signalling or adhesion/invasion (n=19)**

E-cadherin, CD44, CD44v8-10, CD40L, Cytokeratin 10, CD9, caveolin-1,-2, Mapsin, Prostaglandin dehydrogenase, GLUT-1, CA9, Cytokeratin 18 positive cells in bone marrow, Cathepsin B, Rho/ROCK pathway, TATI, MMP-2, MMP-9, HSP-70, Interferon- $\gamma$





PROGNOSTIC MARKERS FOR BLADDER CANCER:  
INTERNATIONAL CONSENSUS PANEL ON BLADDER  
TUMOR MARKERS

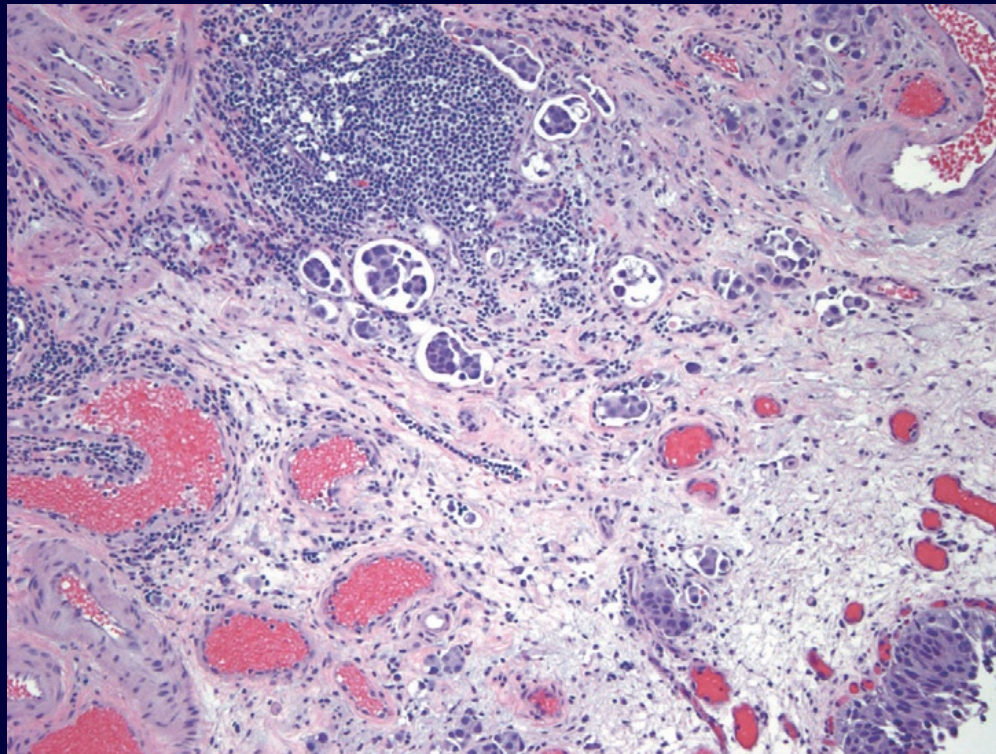
TOMONORI HABUCHI, MICHAEL MARBERGER, MICHAEL J. DROLLER,  
GEORGE P. HEMSTREET III, H. BARTON GROSSMAN, JACK A. SCHALKEN,  
BERND J. SCHMITZ-DRÄGER, WILLIAM M. MURPHY, ALDO V. BONO, PETER GOEBELL,  
ROBERT H. GETZENBERG, STEFAN H. HAUTMANN, EDWARD MESSING, YVES FRADET, AND  
VINATA B. LOKESHWAR

- Αν και κάποιοι μοριακοί δείκτες (**p53, Ki-67, Rb, EGFR, E-cadherin, cyclins, p21, Kip1, apoptosis-related molecules**) φαίνεται να σχετίζονται με την εξέλιξη της νόσου, χρειάζονται πολυκεντρικές μελέτες με standard μεθοδολογία προκειμένου κάποιοι από αυτούς να χρησιμοποιηθούν στη κλινική πράξη
- Για την ώρα δεν υπάρχει κάποιος δείκτης ικανός να καθορίσει τη θεραπευτική απόφαση

# T1HG - Early cystectomy

**LYMPHOVASCULAR INVASION IS AN INDEPENDENT PREDICTOR OF SURVIVAL IN CT1 BLADDER CANCER**

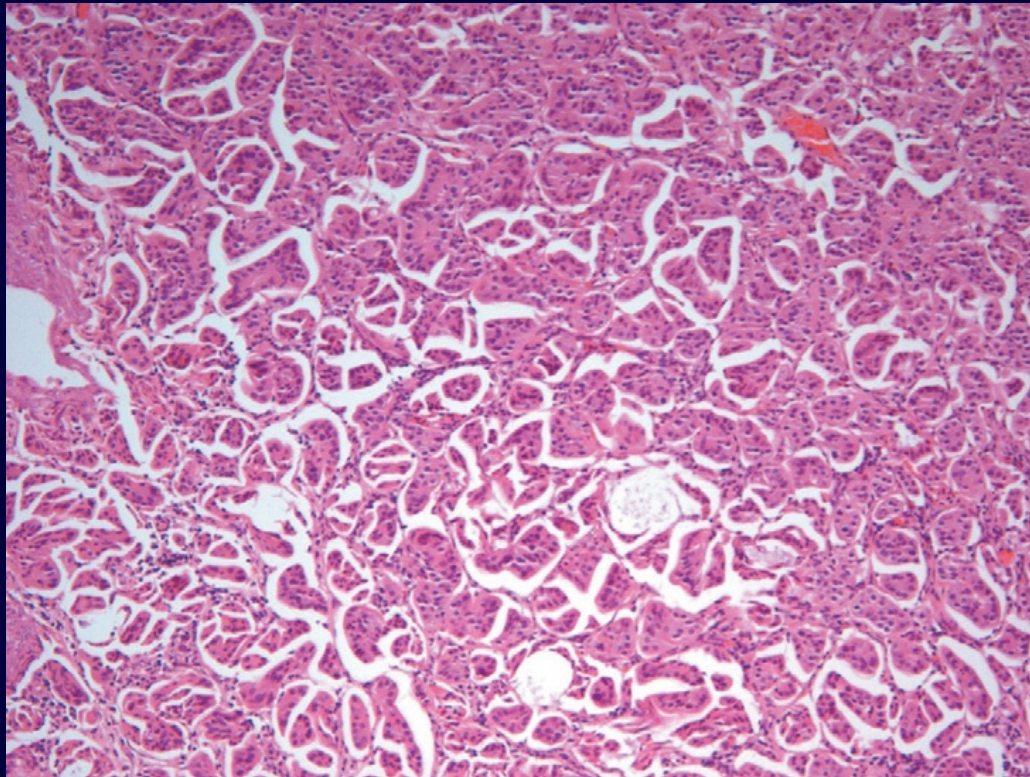
*Cheryl T Lee* et al. AUA 2005: Abstract # 911



# T1HG - Early cystectomy

## THE CASE FOR EARLY CYSTECTOMY IN NON-MUSCLE- INVASIVE MICROPAPILLARY TRANSITIONAL CELL CARCINOMA OF THE BLADDER

*Ashish M Kamat et al. AUA 2005: Abstract #915*





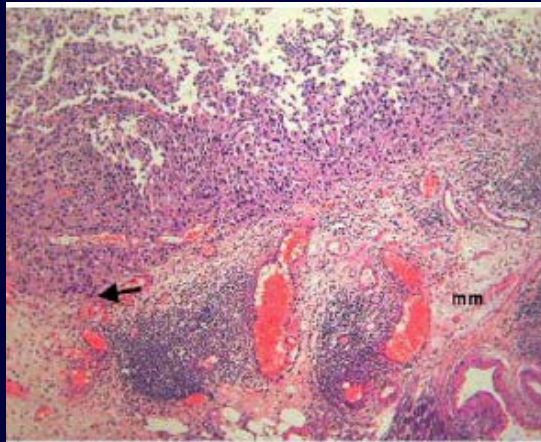
# T1HG-Early cystectomy

## Initial High-Grade T1 Urothelial Cell Carcinoma: Feasibility and Prognostic Significance of Lamina Propria Invasion Microstaging (T1a/b/c) in BCG-Treated and BCG-Non-Treated Patients

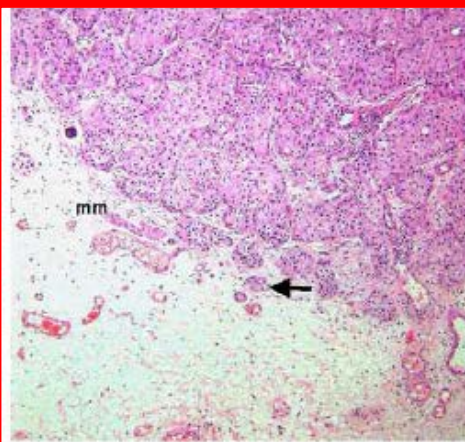
A. Orsola<sup>a,\*</sup>, I. Trias<sup>b</sup>, C.X. Raventós<sup>a,1</sup>, I. Español<sup>b</sup>, L. Cecchini<sup>a,1</sup>, S. Búcar<sup>a</sup>, D. Salinas<sup>a</sup>, I. Orsola<sup>a</sup>

<sup>a</sup>Urology Department, Clínica Plató, Plato 2, 08006, Barcelona, Spain

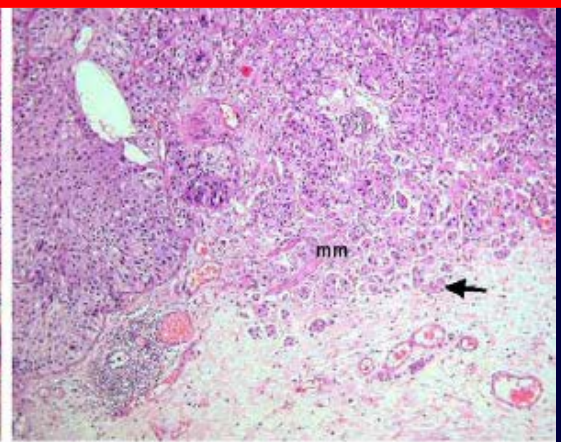
<sup>b</sup>Pathology Department, Clínica Plató, Barcelona, Spain



T1a



T1b



T1c

# T1b-c HG- Early cystectomy

Year	Author	Staging system	Number of cases	Progression (%)	Survival (%)
1990	Younes et al. [6]	T1a (lamina propria)	15	NA	75
		T1b (into MM)	3		
		T1c (across MM)	14		
1994	Hasui et al. [8]	T1a (Younes T1a)	60 <sup>a</sup>	6.7	95
		T1b (Younes T1b and c)	28 <sup>a</sup>	53.5	82
1995	Angulo et al. [21]	T1a (Younes T1a and b)	50 <sup>a</sup>	NA	86
		T1b (Younes T1c)	49 <sup>a</sup>	NA	52
1997	Holmäng et al. [9]	T1a (Younes T1a)	26	36	58
		T1b (Younes T1b and c)	38	58	42
1998	Smits et al. [10]	T1a	119 total <sup>a</sup>	6	NA
		T1b		33	NA
		T1c		55	NA
1998	Hermann et al. [22]	T1a	31 <sup>b</sup>	NA	79
		T1b	60 <sup>b</sup>	NA	70
		T1c	52 <sup>b</sup>	NA	57
1999	Cheng et al. [11]	T1 above MM	23 <sup>a</sup>	11	NA
		T1 into or below MM	21 <sup>a</sup>	32	NA
2000	Kondylis et al. [7]	T1a into MM	32 <sup>b</sup>	22	NA
		T1b beyond MM	17 <sup>b</sup>	29	NA
2001	Bernardini et al. [20]	T1a (Younes T1a)	54 <sup>a</sup>	c	NA
		T1b (Younes T1b and c)	40 <sup>a</sup>		NA
2003	Trias et al. [12]	T1a (Younes T1a)	11	9	NA
		T1b (Younes T1b and c)	13	30.7	NA

NA: not available.

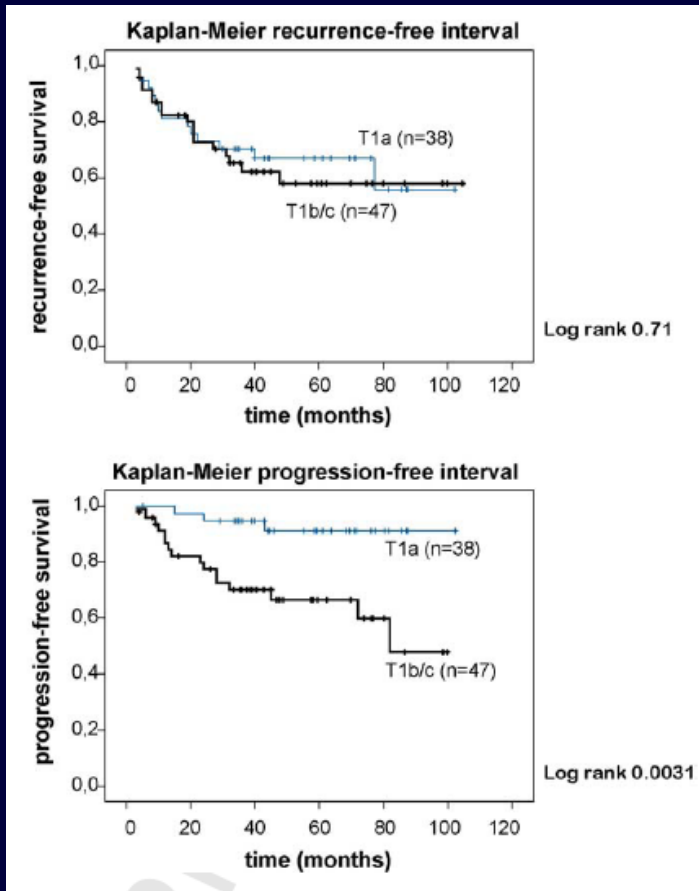
<sup>a</sup>Includes grades 1, 2 and 3.

<sup>b</sup>Includes grades 2 and 3.

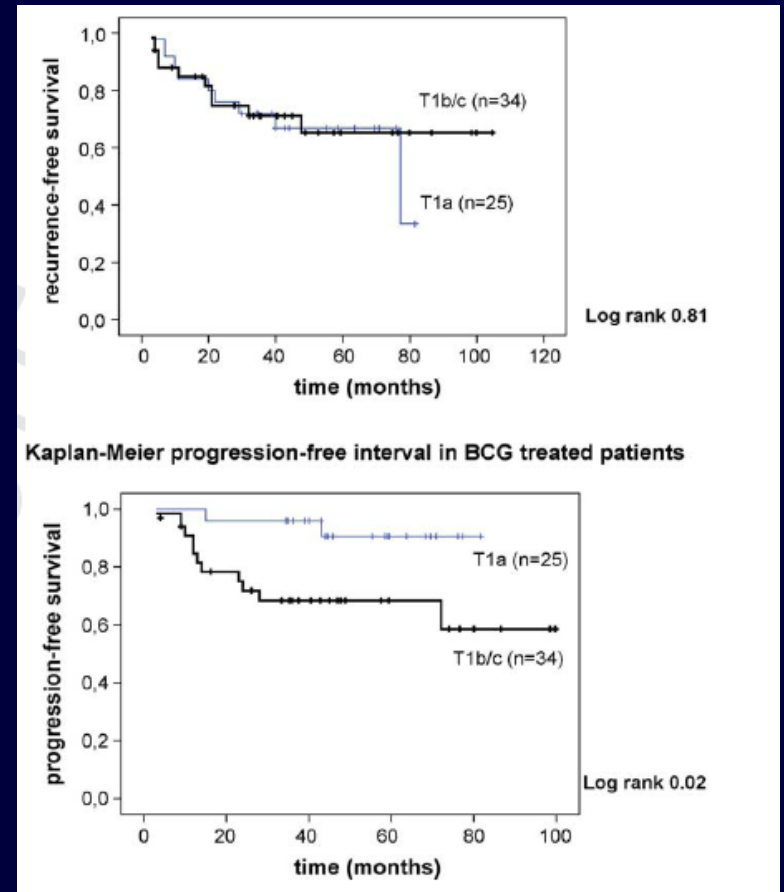
<sup>c</sup>T1b with CIS had risk of progression increased by a factor of 7.5.

# T1b-c HG-Early cystectomy

All pts

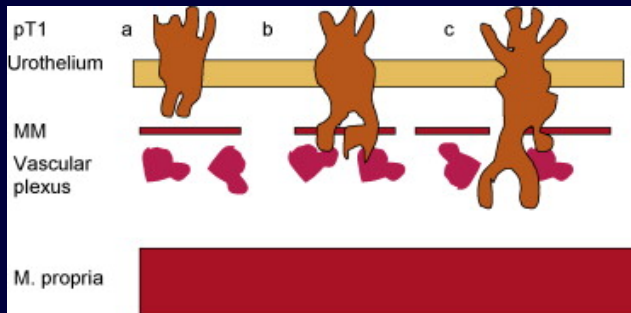


BCG treated pts



# Υποσταδιοποίηση pT1

- Δεν είναι εφικτή στο 35% των περιπτώσεων



- Έχει προταθεί εναλλακτικά η μέτρηση του βάθους διήθησης του χορίου με όριο το 1,5 mm

Bas W.G. van Rhijn et al. Eur Urol. 56;430,2009

Cheng L, et al. J Clin Oncol 1999;17:3182-7

# Δυσμενείς προγνωστικοί παράγοντες σε T1HG

- Συνυπάρχον CIS
- pT1 στη Re-TUR
- Διήθηση προστάτη, προστατικών πόρων
- pT1b
- Λεμφαγγειακή διήθηση (LVI)
- Μικροθηλωματώδης μορφολογία (micropapillary)

Subgroup of highest-risk tumours	T1G3 associated with concurrent bladder CIS, multiple and/or large T1G3 and/or recurrent T1G3, T1G3 with CIS in prostatic urethra, micropapillary variant of urothelial carcinoma	Cystectomy should be considered
	BCG refractory tumours	Cystectomy is recommended



**BREAKING  
NEWS**

May be tomorrow !!!!!



Article

## MicroRNA Expression Profile Identifies High Grade, Non-Muscle-Invasive Bladder Tumors at Elevated Risk to Progress to an Invasive Phenotype

Sara M. Lenherr <sup>1,†</sup>, Sheamei Tsai <sup>1,†</sup>, Brasil Silva Neto <sup>1,2</sup>, Travis B. Sullivan <sup>3</sup>,  
Cara B. Cimmino <sup>1</sup>, Tanya Logvinenko <sup>4,†</sup>, Jason Gee <sup>1</sup>, Wei Huang <sup>5</sup>, John A. Libertino <sup>1</sup>,  
Ian C. Summerhayes <sup>1,3,6</sup> and Kimberly M. Rieger-Christ <sup>1,3,\*</sup>

### 5. Conclusions

We have identified miRNAs associated with a progressive phenotype and survival in UCB, and several of these miRNAs have been linked with EMT. Specifically, levels of miR-203a-3p and miR-205-5p correlated with the degree of invasiveness of the tumor samples, and both miRNAs were significantly associated with time to progression. Two miRNAs (miR-412-3p and miR-224-5p) were significantly associated with time to death from UCB. In addition, a preliminary analysis comparing patients with and without intravesical therapy revealed specific miRNAs differentially expressed between these groups. These could serve as a basis for further research into potential therapeutic agents.

# Συμπληρωματική Ενδοκυστική Ανοσοθεραπεία -BCG

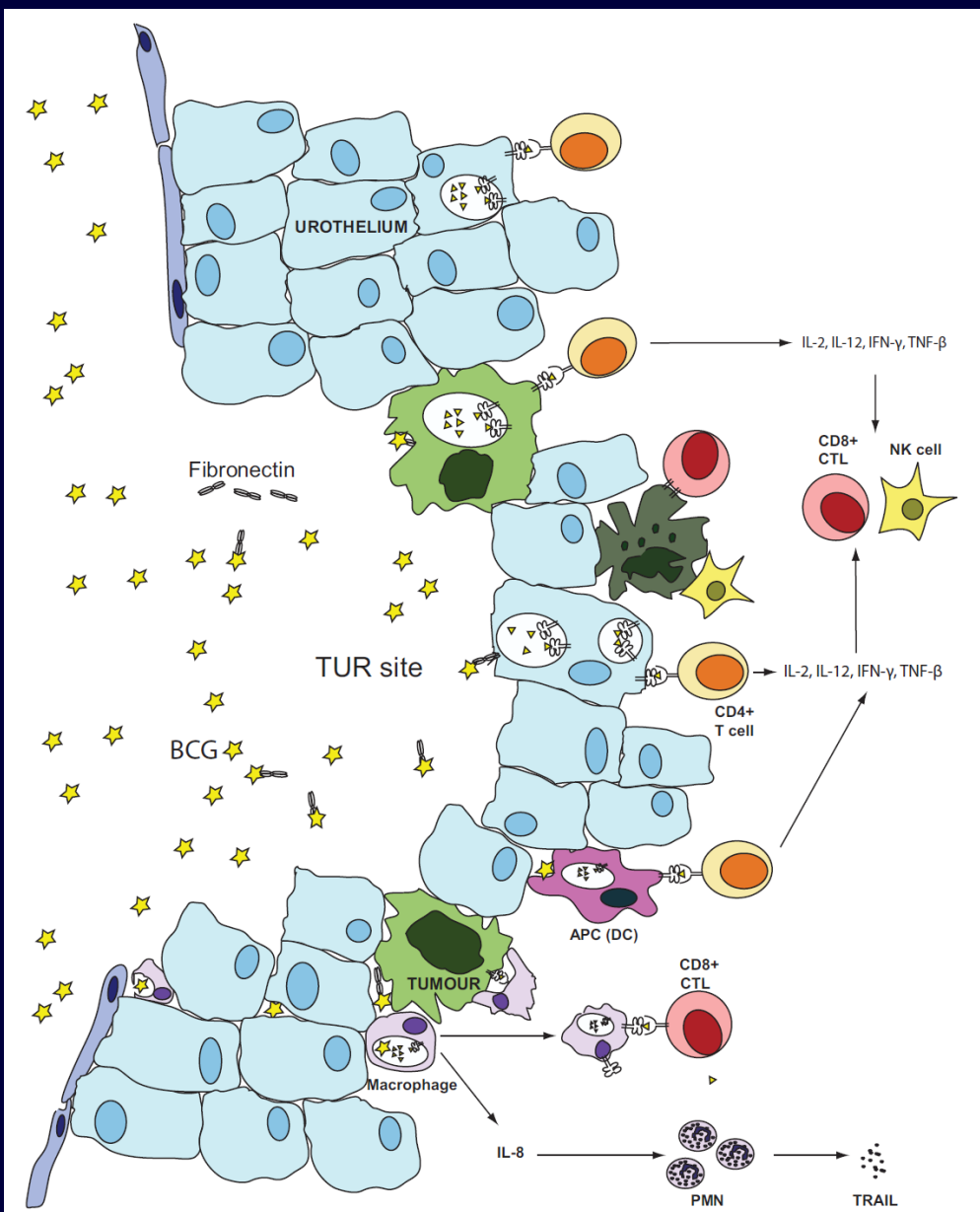
- **Bacillus Calmette-Guerin**
  - Live, attenuated  
*Mycobacterium bovis*
  - Developed by Albert Calmette and Camille Guerin at the Pasteur Institute
    - Used initially as a Tb vaccine
  - Massive local immune response
  - Direct binding of fibronectin  
within the bladder wall



**A. Morales**

*J Urol 1976 Aug;116(2):180-3*

# Bacillus Calmette-Guerin (BCG)–induced immune response



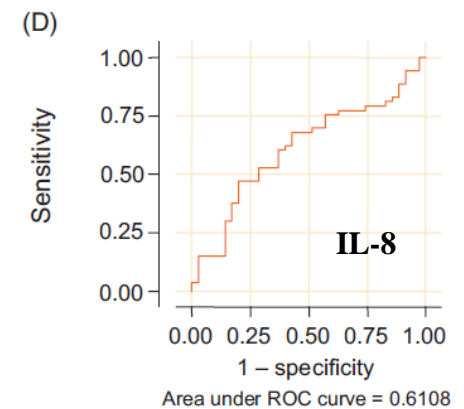
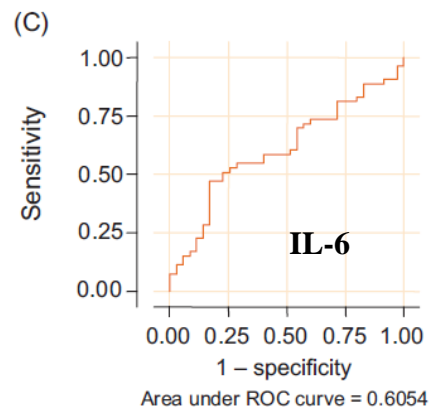
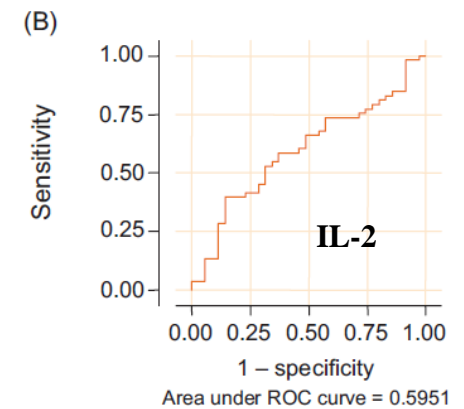
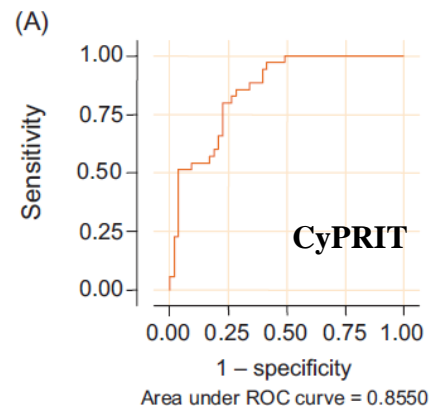
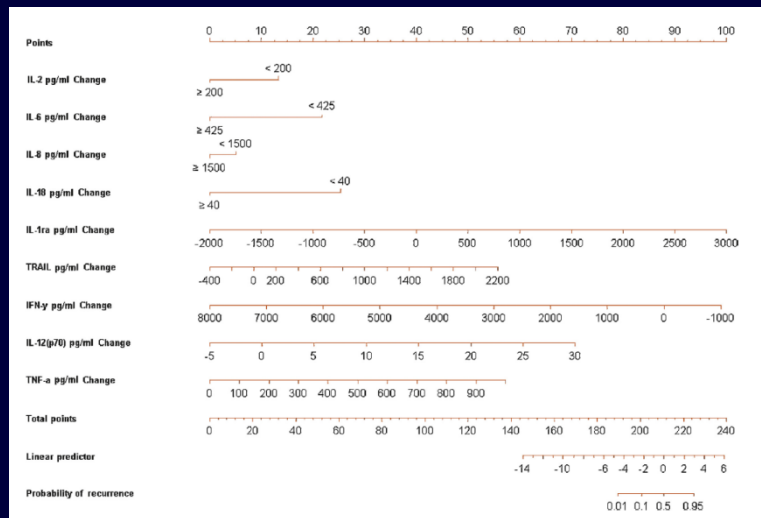
## Conclusions

The most potent marker currently seems to be the measurement of urinary IL-2, whereby high levels of this cytokine after BCG treatment correlate with a more favourable outcome.

# **Cytokine Panel for Response to Intravesical Therapy (CyPRIT): Nomogram of Changes in Urinary Cytokine Levels Predicts Patient Response to Bacillus Calmette-Guérin**

*Ashish M. Kamat<sup>a,\*</sup>, Joseph Briggman<sup>b</sup>, Diana L. Urbauer<sup>c</sup>, Robert Svatek<sup>a</sup>,  
Graciela M. Nogueras González<sup>c</sup>, Roosevelt Anderson<sup>a</sup>, H. Barton Grossman<sup>a</sup>,  
Ferran Prat<sup>d</sup>, Colin P. Dinney<sup>a</sup>*

# Cytokine Panel for Response to Intravesical Therapy (CyPRIT): Nomogram of Changes in Urinary Cytokine Levels Predicts Patient Response to Bacillus Calmette-Guérin



**BCG**

**Induction**

(Δόση εφόδου x 6 εβδομάδες)

+

**Maintenance**

(Συντήρηση για 1-3 έτη)

# BCG vs. CHEMO

## Recurrence Rate

- **5 Meta-analyses: BCG better than TUR alone /TUR + Chemo to reduce Rec. Rate**

*Shelley MD BJU Int 2001, Han RF, Urology 2006., Shelley MD, BJU Int 2004., Böhle A, J Urol 2003, Malmström P-U, Eur Urol 2009*

- **MMC vs, BCG ( 2,820pts. /9 RCTs) :**
  - BCG + Maintenance: ↓ 32% Rec. Rate (p< 0,0001)
  - BCG without Maintenance: ↑ 28% Rec.Rate (p<0,006)

*Malmström P-U, et al.. Eur Urol 2009 Aug;56(2):247-56.*

# BCG vs. CHEMO

## Progression Rate

- 2 Meta-analyses: TUR + BCG delays or prevents progression vs. TUR alone/+chemo

*Böhle A, Urology 2004, Sylvester RJ, J Urol 2002*

- One recent RCT with long-term f/u: BCG vs. epirubicin : ↓ distant metastases, ↑ DSS, OS

*Sylvester RJ, et al. Eur Urol 2010 May;57(5):766-73*

- 1 recent meta-analysis of pts data: BCG vs. MMC : No difference in progression rate, survival, cause of death

*Malmström P-U, et al.. Eur Urol 2009 Aug;56(2):247-56.*



# **INTRAVESICAL BACILLUS CALMETTE-GUERIN REDUCES THE RISK OF PROGRESSION IN PATIENTS WITH SUPERFICIAL BLADDER CANCER: A META-ANALYSIS OF THE PUBLISHED RESULTS OF RANDOMIZED CLINICAL TRIALS**

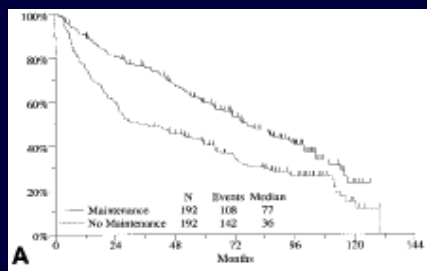
**RICHARD J. SYLVESTER, et al. J Urol 2002;168:1964-1970**

- Median F.U : 2,5 years (1,6-15 yrs)
- Progression rate: papillary tumors: 6,4% (n=2.880 pts),  
CIS : 13,9% (n=403 pts)
- BCG vs. Control/ Reduction of progression:  
9,8% vs. 13,8% (OR: 0,73, p=0,001)
- BCG reduces the risk of progression when BCG maintenance treatment is used
- **No conclusions about the risk of bladder cancer death. Death due to bladder cancer in case of progression is 64% in 2,5 years**
- No large differences between BCG strains
- BCG induced cystitis : 91% of cases

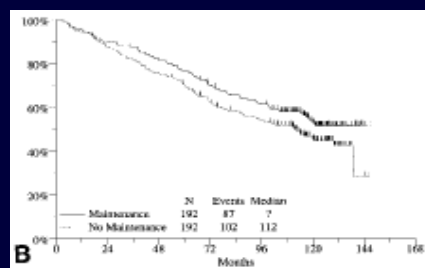
**“BCG is the drug of choice for intermediate and high risk papillary tumors and the best intravesical treatment for CIS”**

# MAINTENANCE BACILLUS CALMETTE-GUERIN IMMUNOTHERAPY FOR RECURRENT TA, T1 AND CARCINOMA IN SITU TRANSITIONAL CELL CARCINOMA OF THE BLADDER: A RANDOMIZED SOUTHWEST ONCOLOGY GROUP STUDY

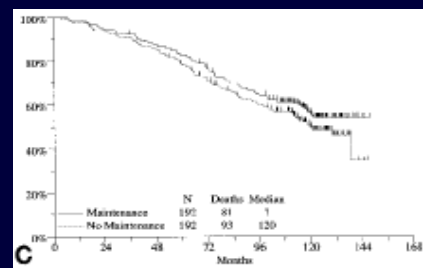
DONALD L. LAMM, et al. J Urol.2000;163: 1124-1129



**Recurrence Free surv.**



**Progression Free surv.**



**Overall 5 year surv.**

## “SWOG 3+3+6”

- Median Recurrence Free Survival: 35,7 months vs. 76,8 months (p<0,0001)
- Median Progression Free Survival: 111,5 m. vs . not estimable (p<0,04)
- Overall 5 year Survival: 78% vs. 83% (p=0,08)

Only 16% of the 243 maintenance cases received all 8 scheduled maintenance courses during 3 years.

# BCG toxicity

- BCG: μεγαλύτερη τοξικότητα από την ΧΜΘ
- Σοβαρές επιπλοκές: <5% των ασθενών

Management options for local side effects (modified from IBCG group)	
Symptoms of cystitis	Phenazopyridine, propantheline bromide, or NSAIDs
	If symptoms improve within a few days: continue instillations
	If symptoms persist or worsen: <ol style="list-style-type: none"> <li>Postpone the instillations</li> <li>Perform a urine culture</li> <li>Start empirical antibiotic treatment</li> </ol>
	If symptoms persist even with antibiotic treatment: <ol style="list-style-type: none"> <li>With positive culture: antibiotic treatment according to sensitivity.</li> <li>With negative culture: quinolones and potentially analgesic anti-inflammatory instillations once daily for 5 days (to repeat cycle if necessary) (173).</li> </ol>
	If symptoms persist: anti-tuberculosis drugs + corticosteroids.
	If no response to treatment and/or contracted bladder: radical cystectomy.
Haematuria	Perform urine culture to exclude haemorrhagic cystitis, if other symptoms present.
	If haematuria persists, perform cystoscopy to evaluate presence of bladder tumour.
Symptomatic granulomatous prostatitis	Symptoms rarely present: perform urine culture.
	Quinolones.
	If quinolones are not effective: isoniazid (300 mg/day) and rifampicin (600 mg/day) for 3 months.
	Cessation of intravesical therapy.
Epididymo-orchitis (172)	Perform urine culture and administer quinolones.
	Cessation of intravesical therapy.
	Orchidectomy if abscess or no response to treatment.

Management options for systemic side effects	
General malaise, fever	Generally resolve within 48 h, with or without antipyretics.
Arthralgia and/or arthritis	Rare complication and considered autoimmune reaction.
	Arthralgia: treatment with NSAIDs.
	Arthritis: NSAIDs and if no/partial response proceed to corticosteroids, high-dose quinolones or antituberculous drugs (171).
Persistent high-grade fever (> 38.5°C for > 48 h)	Permanent discontinuation of BCG instillations.
	Immediate evaluation: urine culture, blood tests, chest X-ray.
	Prompt treatment with ≥ 2 antimicrobial agents while diagnostic evaluation is conducted.
	Consultation with an infectious diseases specialist.
BCG sepsis	Prevention: initiate BCG at least 2 weeks post TURBT (if no signs and symptoms of haematuria).
	Cessation of BCG
	For severe infection: <ul style="list-style-type: none"> <li>- High-dose quinolones or isoniazid, rifampicin and ethambutol 1.2 g daily for 6 months.</li> <li>- Early, high-dose corticosteroids as long as symptoms persist.</li> </ul> Consider an empirical non-specific antibiotic to cover Gram-negative bacteria and/or Enterococcus.
Allergic reactions	Antihistamines and anti-inflammatory agents.
	Consider high-dose quinolones or isoniazid and rifampicin for persistent symptoms.
	Delay therapy until reactions resolve.

## BCG δεν πρέπει να γίνεται σε...

- Τις πρώτες 15 ημέρες μετά το TUR
- Ασθενείς με μακροσκοπική αιματουρία
- Μετά από τραυματικό καθετηριασμό
- Σε ασθενείς με συμπτωματική λοίμωξη ουροποιητικού
- Σε ασθενείς ανοσοκατασταλμένους (σχετική αντένδειξη)

## Increasing age is not associated with toxicity leading to discontinuation of treatment in patients with urothelial non-muscle-invasive bladder cancer randomised to receive 3 years of maintenance bacille Calmette–Guérin: results from European Organisation for Research and Treatment of Cancer Genito-Urinary Group study 30911

Jorg R. Ouddens<sup>\*</sup>, Richard J. Sylvester<sup>†</sup>, Maurizio A. Brausi<sup>‡</sup>, Wim J. Kirkels<sup>§</sup>, Cees van de Beek<sup>¶</sup>, George van Andel<sup>\*\*</sup>, Theo M. de Reijke<sup>††</sup>, Stephen Prescott<sup>‡‡</sup>, J. Alfred Witjes<sup>§§</sup> and Willem Oosterlinck<sup>¶¶</sup>

	Age group, years				Total n (%)
	≤60 n (%)	61–70 n (%)	71–75 n (%)	>75 n (%)	
Not stopped due to toxicity	110 (82.1)	146 (78.1)	81 (77.1)	51 (83.6)	388 (79.7)
Stopped due to toxicity	24 (17.9)	41 (21.9)	24 (22.9)	10 (16.4)	99 (20.3)



# Maintenance: Optimal BCG dose

- RCT: 500pts CUETO group / Full dose vs. 1/3 dose:
  - ✓ No overall difference in efficacy
  - ✓ Full dose better in m/f tumors
  - ✓ Lower toxicity with 1/3 dose
  - ✓ Same Risk of severe systemic toxicity

*Martinez-Pineiro JA et al. BJU Int 2002.,J Urol 2005.*

- RCT: 1/3 dose the minimum effective dose for intermediate risk NMI BCa

*Ojea A, et al. Eur Urol 2007 Nov;52(5):1398-406.*

- EORTC: Full vs. 1/3 dose: No difference in toxicity
  - ✓ 1/3 dose for only 1 yr: ↑ Recurrence Rate

*Oddens J,et al. Eur Urol 2013 Mar;63(3):462-72*

**BCG**

**+**

**Maintenance (Συντήρηση)**

**In patients with high-risk tumours, full-dose intravesical BCG for 1-3 years is indicated.**

**(Grade of recommendation: A)**

**EAU Guidelines**

# **BCG Failure**

# BCG Failure σε T1GIII

Results of TUR plus BCG for T1G3 tumors

Series/year	No. patients	Follow-up (mo)	Recurrence (%)	Progression (%)
Pfister (1995)	26	54	50	27
Lebret (1998)	35	45	43	20
Brake (2000)	44	43	27	16
Patard (2001)	50	65	52	22
Kulkarni (2002)	69	48	46	12
Bogdanovic (2002)	43	53	28	16
Peyromaure (2003)	57	53	42	23
Shanin (2003)	92	64	70	33

## T1 G3- BCG Failure at 5-yrs

- **Recurrence : ~ 50%**
- **Progression : 12-33%**

# BCG Failure

Herr and Dalbagni J Urol 69: 1706–1708, 2003

- *BCG-refractory disease* (ανίατος)

failure to achieve a disease-free state by 6 months after initial BCG therapy with either maintenance or retreatment at 3 months

- *BCG-resistant disease* (αντοχή)

recurrence or persistence of disease at 3 months after the induction cycle. It is of lesser degree, stage, or grade, and is no longer present at 6 months from BCG retreatment

- *BCG-relapsing disease* (υποτροπή)

recurrence of disease after achieving a disease-free status by 6 months . Relapse is further defined by time of recurrence as *early* (within 12 months), *intermediate* (12 to 24 months), or *late* (24months).

- *BCG-intolerant disease* (δυσανεξία)

recurrent disease in setting of inadequate BCG treatment because of drug toxicity



# BCG Failure

- *BCG-refractory disease* → Cystectomy
- *BCG-resistant disease* → ?
- *Early BCG-relapsing disease* → Cystectomy
- *Intermediate, late* → ?
- *BCG-intolerant disease* → ?

# BCG Failure

## BCG failure

Whenever a muscle-invasive tumour is detected during follow-up.

BCG-refractory tumour:

1. If high-grade, non-muscle-invasive papillary tumour is present at 3 months (185). Further conservative treatment with BCG is connected with increased risk of progression (122,186) (LE: 3).
2. If CIS (without concomitant papillary tumour) is present at both 3 and 6 months. In patients with CIS present at 3 months, an additional BCG course can achieve a complete response in > 50% of cases (42) LE: 3).
3. If high-grade tumour appears during BCG therapy.\*

High grade recurrence after BCG. Recurrence of high grade/grade 3 (WHO 2004/1973) tumour after completion of BCG maintenance, despite an initial response (187) (LE: 3).\*

## BCG intolerance

Severe side effects that prevent further BCG instillation before completing induction (170).

*\* Patients with low-grade recurrence during or after BCG treatment are not considered as BCG failure.*

**SOS**

# BCG Failure- Cystectomy

Category	Treatment recommendation	GR
BCG refractory tumour	<ol style="list-style-type: none"><li>1. Radical cystectomy</li><li>2. Bladder-preserving strategies in patients not suitable for cystectomy</li></ol>	B
High-grade recurrence after BCG	<ol style="list-style-type: none"><li>1. Radical cystectomy</li><li>2. Repeat BCG course</li><li>3. Bladder-preserving strategies</li></ol>	C
Non-high-grade recurrence after BCG for primary intermediate-risk tumour	<ol style="list-style-type: none"><li>1. Repeat BCG or intravesical chemotherapy</li><li>2. Radical cystectomy</li></ol>	C

# **BCG failure**

## **Second-line intravesical therapy**

**2<sup>nd</sup> line BCG (response: 50%)**

**BCG+INF-A2b**

**Optimization of intravesical chemotherapy**

**Local microwave hyperthermia + MMC (Synergo)**

**Photodynamic Therapy (5-ALA)**

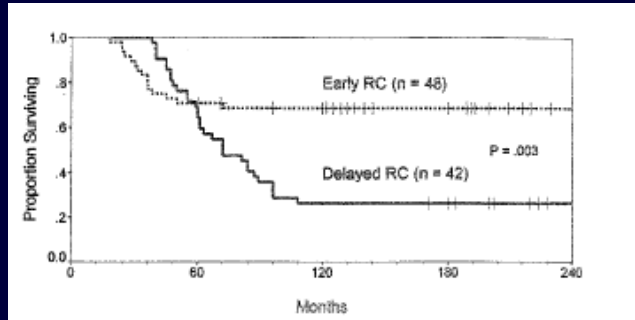
**Intravesical Gemcitabine, Docetaxel**

**“Oncologically inferior than RC”**

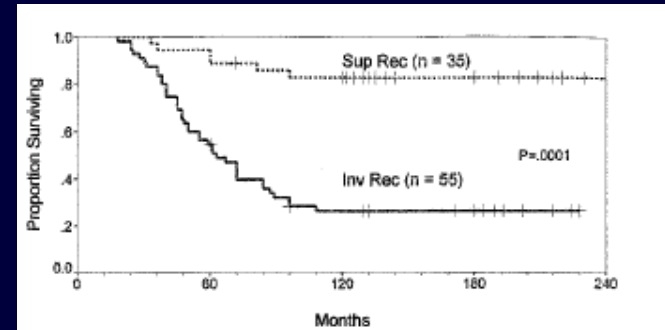
# T1 GII – BCG FAILURE

## Early vs. delayed cystectomy

H. HERR AND P.C. SOGANI, J Urol.2001 ; 166: 1296–1299



**Vs.**

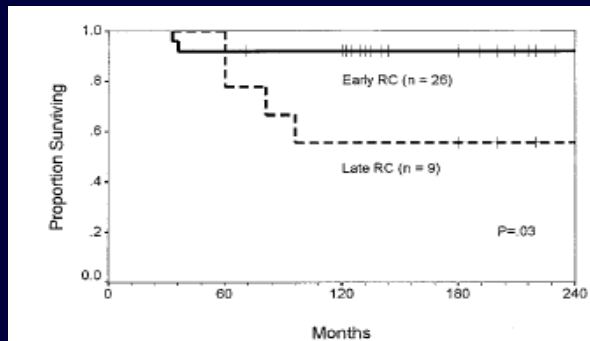


**pT0: Early 33pts, Delayed 11pts**  
**DOD: Early 15 pts, Delayed 31 pts**

**Mortality:**  
**2,5%**

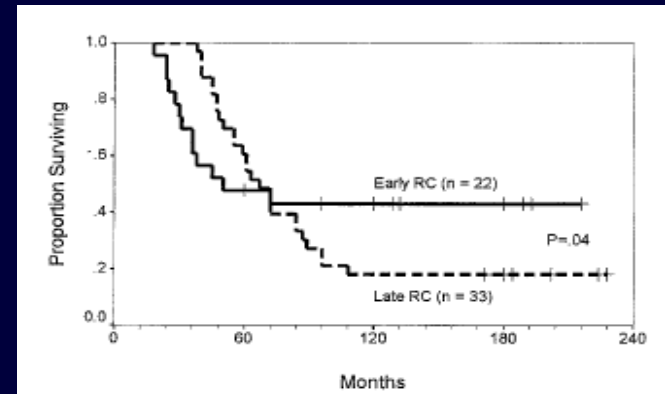
**pT0: Early 29pts, delayed 15pts**  
**DOD: Early 6 pts, Delayed 40 pts**

**Morbidity:**  
**28%**



**Recurrent SBC**

**pT0: Early 24pts, Delayed 5pts**  
**DOD: Early 2 pts, Delayed 4 pts**



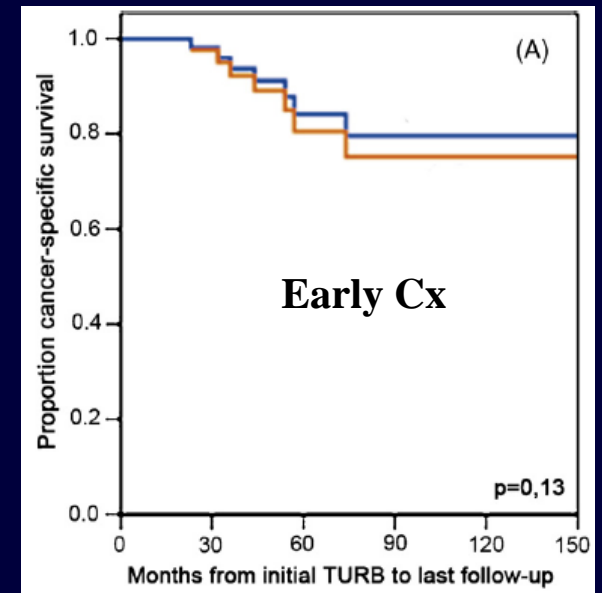
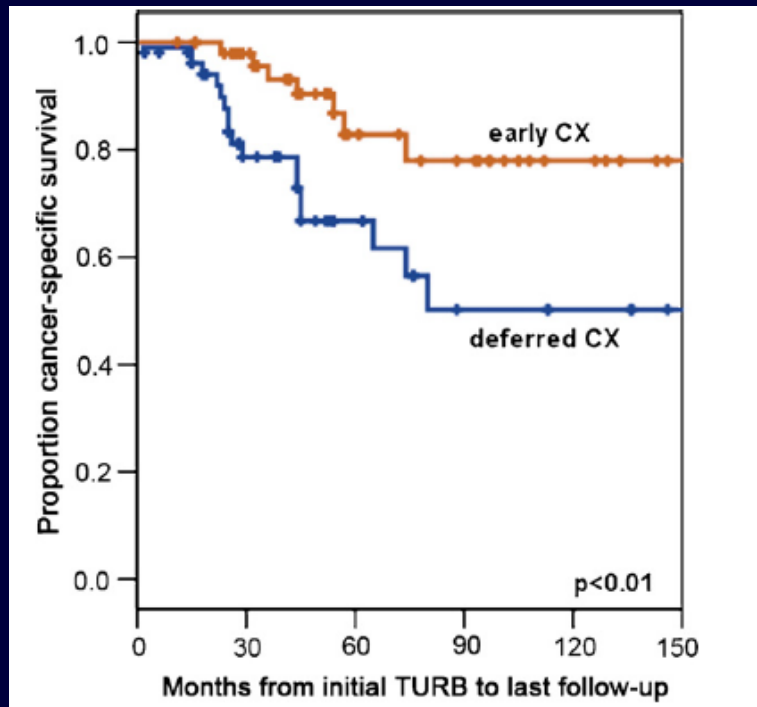
**Progressed Invasive Ca**

**pT0: Early 9pts, Delayed 6pts**  
**DOD: Early 13 pts, Delayed 27 pts**

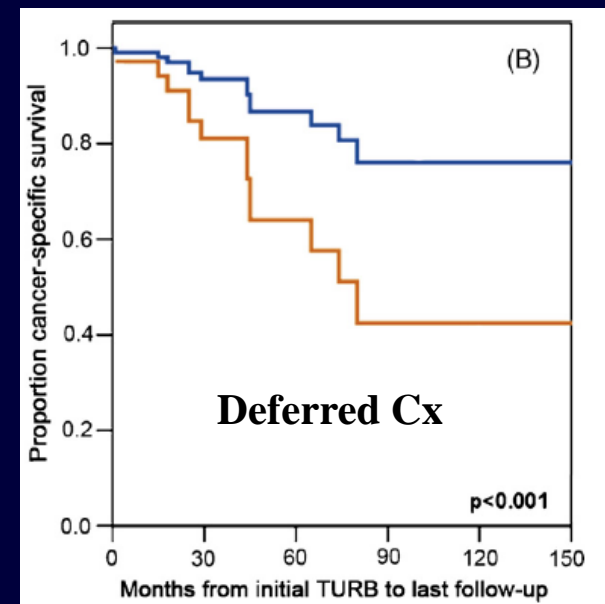


# Early Versus Deferred Cystectomy for Initial High-Risk pT1G3 Urothelial Carcinoma of the Bladder: Do Risk Factors Define Feasibility of Bladder-Sparing Approach?

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



**T1G3 +/- CIS**



# Ριζική Κυστεκτομή στον μη διηθητικό καρκίνο της κύστεως. Πότε;

- Η 5ετής επιβίωση της τάξης του 90% μπορεί να υποχωρήσει στο 50-60% αν η κυστεκτομή καθυστερήσει μέχρι την πρόοδο της νόσου.

*Malkowicz BS, et al. J Urol 1990;144:641*

- Καλύτερη ειδική για τη νόσο επιβίωση (15ετία) σε ασθενείς με T1HG που υποβλήθηκαν σε άμεση κυστεκτομή vs κυστεκτομή 2 έτη μετά το αρχικό BCG.

*Herr HW, Sogani PC. J Urol 2001;166:1296–9.*

# Κυστεκτομή

**Immediate radical cystectomy may be offered to patients at highest risk of tumour progression. In patients with BCG failure, cystectomy is recommended.**

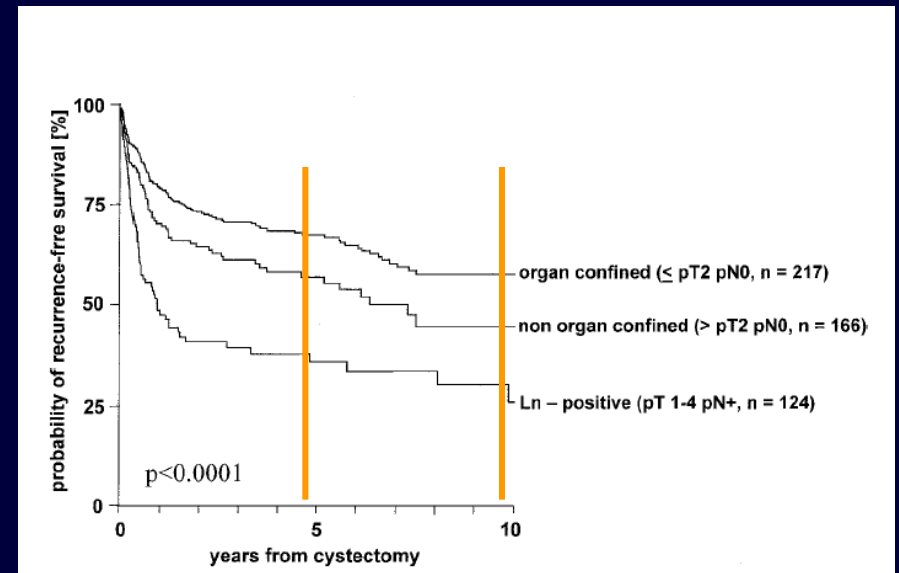
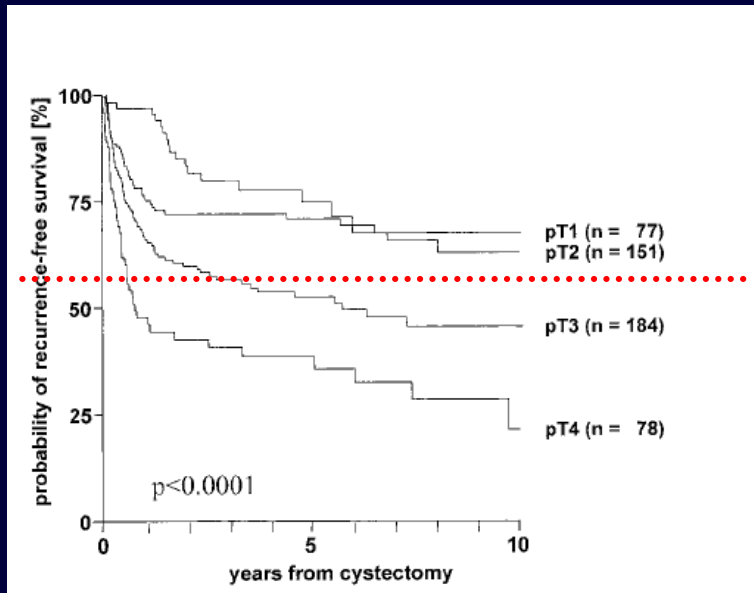
**(Grade of recommendation: C)**

## Κυστεκτομή στον μη-μυοδηθητικό, high grade, καρκίνο κύστης Κλινική υποσταδιοποίηση

STUDY	INSTITUTION	RISK (%) OF UNDERSTAGING
Stein et al, 2001	Southern California	39
Dutta et al, 2001	Vanderbilt University	40
Bianco et al, 2004	Wayne State University	27
Bayraktar et al, 2004	Vakif Gureba Hospital Aksaray-Istanbul, Turkey	50
Huguet et al, 2005	Servicio de Urologia, Fundacion Puigvert, Barcelona	27
Ficarra et al, 2005	University of Verona, Italy	43

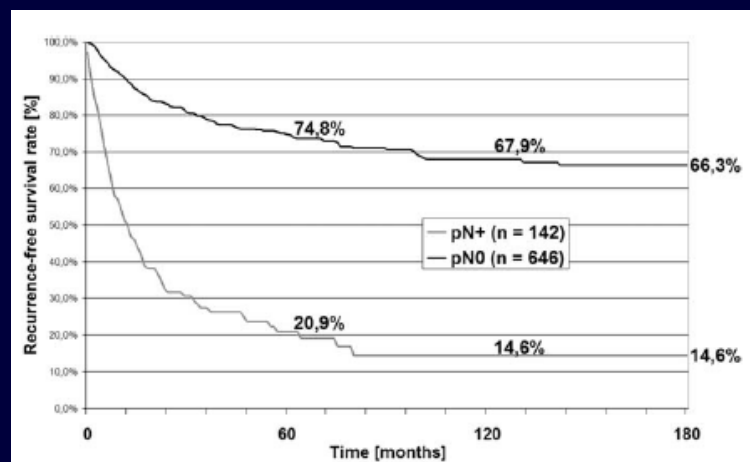
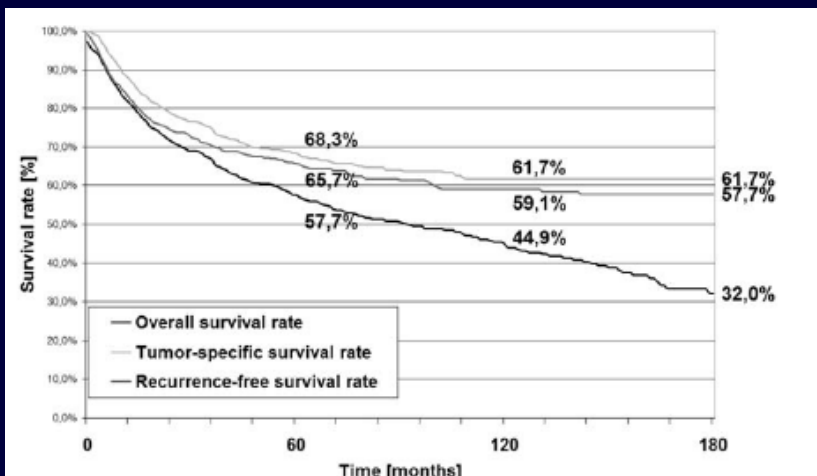
# Ογκολογικό αποτέλεσμα

*Madersbacher, Studer et al, J Clin Oncol 2003; 21:690-696*

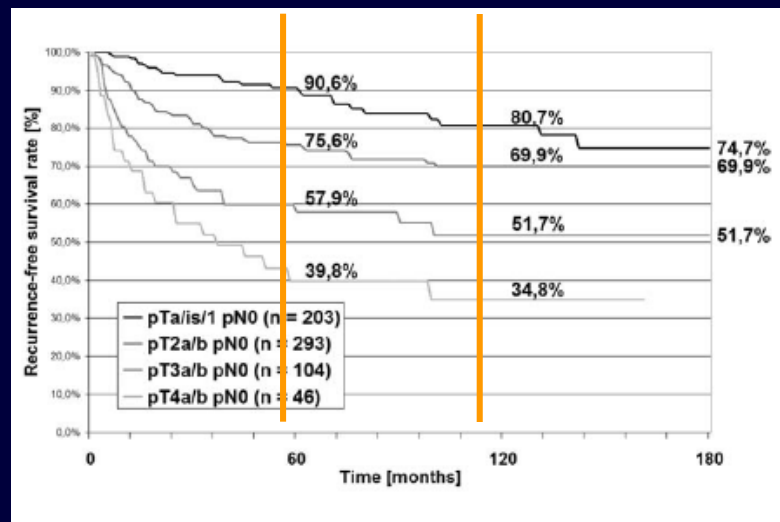
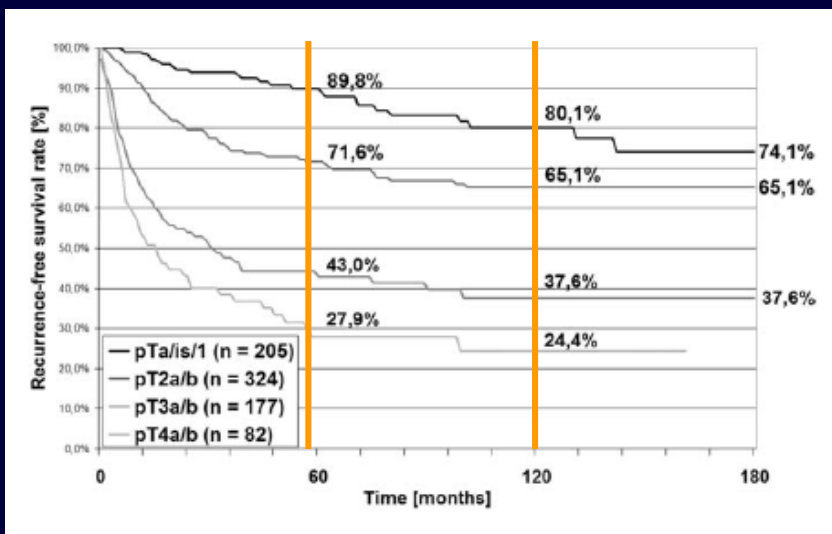




# Ογκολογικό αποτέλεσμα



N=788



## Εξαιρετικός τοπικός έλεγχος της νόσου

Table 2. **Local Recurrence** and Distant Failure According to Tumor Stage

Tumor Stage	NED		Local Recurrence		Distant Failure	
	No.	%	No.	%	No.	%
pTa/pTIS/pT1pN0 (n = 92)	66	72	2	2	24	26
All pTIS/pT1pN0-2 (n = 94)	67	71	2	2	25	27
pT2pN0 (n = 125)	91	73	4	3	30	24
All pT2pN0-2 (n = 151)	105	69	6	4	40	27
pT3pN0 (n = 120)	67	56	9	8	44	37
All pT3pN0-2 (n = 184)	91	49	16	9	77	42
pT4pN0 (n = 46)	20	43	9	20	17	37
All pT4pN0-2 (n = 78)	25	32	16	21	37	47
Organ confined ( $\leq$ pT2pN0; n = 217)	157	72	6	3	54	25
Non-organ confined ( $>$ pT2pN0; n = 166)	87	52	18	11	61	37
All pN+ (n = 124)	44	36	16	13	64	51
Total (n = 507)	288	56	40	8	179	35

Abbreviation: NED, no evidence of disease.

# Κυστεκτομή στον μη-μυοδηθητικό καρκίνο κύστης

Pathologic Stage*	No. of Patients	Recurrence-Free		Overall Survival	
		5 Years	10 Years	5 Years	10 Years
Po, Pa, Pis					
N-#	208	.89 ± .02	.85 ± .03	.85 ± .03	.67 ± .04
N+‡	5	.60 ± .22	.60 ± .22	.40 ± .22	.40 ± .22
All Pts PoPaPis	213	.88 ± .02	.85 ± .03	.84 ± .03	.67 ± .04
P1					
N-	194	.83 ± .03	.78 ± .04	.76 ± .03	.52 ± .04
N+‡	14	.43 ± .13	.43 ± .13	.50 ± .13	.42 ± .13
All Pts P1	208	.80 ± .03	.75 ± .04	.74 ± .03	.51 ± .04
P2					
N-	94	.89 ± .03	.87 ± .04	.77 ± .04	.57 ± .06
N+‡	21	.50 ± .11	.50 ± .11	.52 ± .11	.52 ± .11
All Pts P2	115	.81 ± .04	.80 ± .04	.72 ± .04	.56 ± .05
P3a					
N-	98	.78 ± .05	.76 ± .05	.64 ± .05	.44 ± .06
N+‡	35	.41 ± .09	.37 ± .09	.40 ± .08	.26 ± .08
All Pts P3a	133	.68 ± .04	.65 ± .05	.58 ± .04	.39 ± .05
P3b					
N-	135	.62 ± .05	.61 ± .05	.49 ± .04	.29 ± .05
N+‡	113	.29 ± .05	.29 ± .05	.24 ± .04	.12 ± .04
All Pts P3b	248	.47 ± .04	.46 ± .04	.38 ± .03	.22 ± .03
P4a					
N-	79	.50 ± .06	.45 ± .07	.44 ± .06	.23 ± .06
N+‡	58	.33 ± .07	.33 ± .07	.26 ± .06	.20 ± .05
All Pts P4a	137	.44 ± .05	.41 ± .05	.33 ± .04	.22 ± .04
Organ-confined†					
N-	594	.85 ± .02	.82 ± .02	.78 ± .02	.56 ± .02
N+‡	75	.46 ± .06	.44 ± .06	.45 ± .06	.37 ± .06
All Pts	669	.80 ± .02	.77 ± .02	.74 ± .02	.54 ± .02
Extravesical‡					
N-	214	.58 ± .04	.55 ± .04	.47 ± .04	.27 ± .04
N+‡	171	.30 ± .04	.30 ± .04	.25 ± .04	.17 ± .03
All Pts	385	.46 ± .03	.44 ± .03	.37 ± .03	.22 ± .03
LN- Pts	808	.78 ± .02	.75 ± .02	.69 ± .02	.49 ± .02
LN+ Pts	246	.35 ± .03	.34 ± .03	.31 ± .03	.23 ± .03
Total group	1,054	.68 ± .02	.66 ± .02	.60 ± .02	.43 ± .02

# Κυστεκτομή στον μη-μυοδηθητικό καρκίνο κύστης

*Madersbacher, Studer et al, J Clin Oncol 2003; 21:690-696*

**Table 1. Principal Patient Characteristics (n = 507)**

Characteristic	All Patients		pN0		pN+	
	No.	%	No.	%	No.	%
<b>Pathologic staging</b>						
pTa/pTIS	17	3	17	3	0	0
pT1	77	15	75	15	2	0.4
pT2	151	30	125	25	26	5
pT3	184	36	120	24	64	13
pT4	78	16	46	9	32	6
Total	507	100	383	76	124	24
Grade 1 TCC	3	0.6				
Grade 2 TCC	21	4				
Grade 3 TCC	483	95				
Age, years (mean ± SD)	66 ± 12 (range, 35-89)					
Men (n = 400)	66 ± 9 (range, 36-89)					
Women (n = 107)	64 ± 18 (range, 35-86)					
Median/mean follow-up, months	31/45 (range, 0.1-176)					

*Το 20-40% (περίπου το 1/3) γίνονται σε μη-μυοδηθητικούς High-grade όγκους*

# Ακτινοθ/πεία σε T1HG ?

- T1: 50% 5-yrs DFS
- T1: local recurrence or/and progression :  
50% at 5yrs

Dunst J, et al. Int J Radiat Oncol Biol Phys 1994;30: 261–6

Rodel C, et al. Strahlenther Onkol 2001;177:82–8

MANOHARAN & SOLOWAY. Urol Clin N Am 32 (2005) 133–145

# Παρακολούθηση (f/u) NMI BCa

- Η έγκαιρη διάγνωση της υποτροπής είναι κρίσιμη για την τυχόν εξέλιξη της νόσου και την πορεία του ασθενούς
- Οι υποτροπές των low grade και stage νεοπλασμάτων (Ta G1, GIIa) είναι κατά κανόνα : low grade & stage
- Η πρώτη f/u κυστεοσκόπηση μετά 3 μήνες από την TUR είναι σημαντικός προγνωστικός παράγοντας για την υποτροπή και την εξέλιξη της νόσου



# Παρακολούθηση (f/u) NMI BCa

- Στα low risk η πιθανότητα υποτροπής μετά την 5 ετία είναι χαμηλή.
- Στα intermediate και high risk η πιθανότητα υποτροπής μετά 10 ετία ελεύθερης νόσου δεν είναι σπάνια . Γι αυτό το f/u θα πρέπει να συνεχίζεται δια βίου
- Ο κίνδυνος υποτροπής στο ανώτερο ουροποιητικό (νεφρική πύελο, ουρητήρα) αυξάνεται στα πολυεστιακά και high risk νεοπλάσματα
- Η κυτταρολογική και τα υπόλοιπα urine tests έχουν βοηθητικά θετικό ρόλο στην f/u κυστεοσκόπηση

# Παρακολούθηση (f/u) NMI BCa

High-risk tumours	Any of the following: <ul style="list-style-type: none"><li>• T1 tumour</li><li>• G3 (high grade) tumour</li><li>• CIS</li><li>• Multiple and recurrent and large (&gt; 3 cm) Ta G1G2 tumours (all conditions must be presented in this point)</li></ul>
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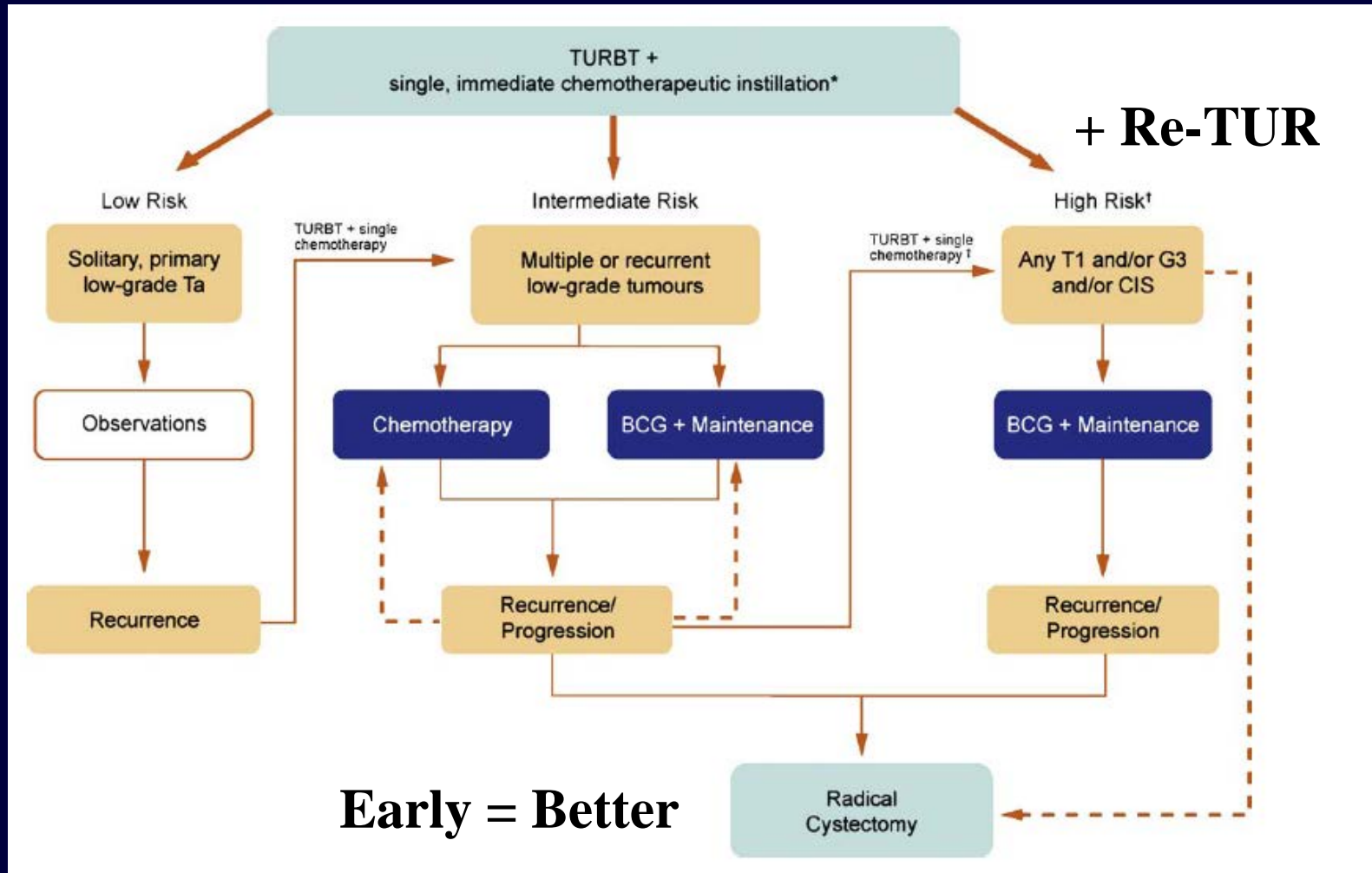
## High Risk :

- ✓ **1<sup>st</sup> f/u urine cytology & cystoscopy at 3 months**
- ✓ **every 3 months f/u urine cytology & cystoscopy for 2 years**
- ✓ **every 6 months f/u urine cytology & cystoscopy for 5 years**
- ✓ **yearly after**
- ✓ **yearly imaging (C/T IVU or IVU ) of upper tract from 1<sup>st</sup> year**

Patients with high-risk tumours should undergo cystoscopy and urinary cytology at 3 months. If negative, subsequent cystoscopy and cytology should be repeated every 3 months for a period of 2 years, and every 6 months thereafter until 5 years, and then yearly.

C

# Συμπεράσματα





*ευχαριστώ*