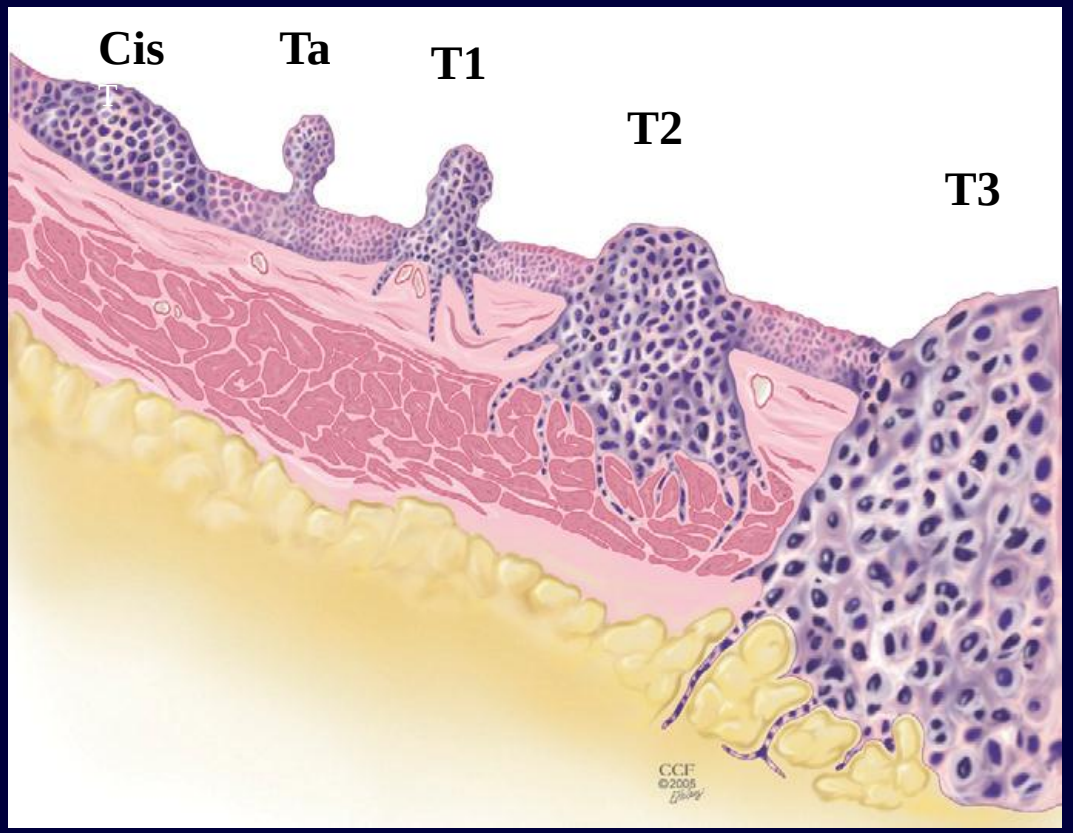
Αντιμετώπιση μη Μυοδηθητικού Καρκίνου Κύστης Υψηλού Κινδύνου (T1G3)

Αλκιβιάδης Γρηγοράκης
Επιμελητής Ουρολογικού Τμήματος
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)

ELSEVIER

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 Calmetle-Guérin*

Study	N	Progression (%)	Follow-up (mo)
Heney *et al.* (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	—

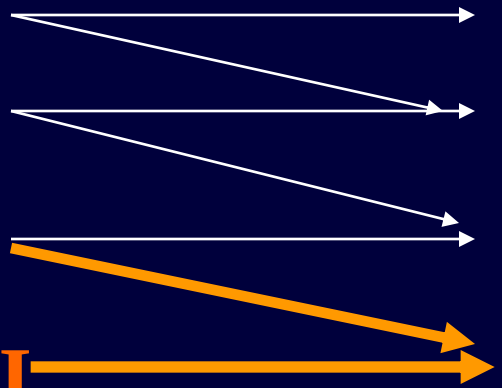
T1 G3 at 5yrs

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

UROLOGY 66 (Suppl 6A): 108–125, 2005

1973 WHO vs.1998 WHO/ISUP

WHO 1973	WHO 1998
Papilloma	Papilloma
Grade I	PUNLMP
Grade II	Low Grade
Grade III	**High Grade**



High Risk non muscle invasive bladder cancer

T1GIII → Χωρίς συμπληρωματική θεραπεία:
Υποτροπή: 50-70%
Εξέλιξη: 25-50%

↓

T1 HG, Ta HG, (mf/r)CIS

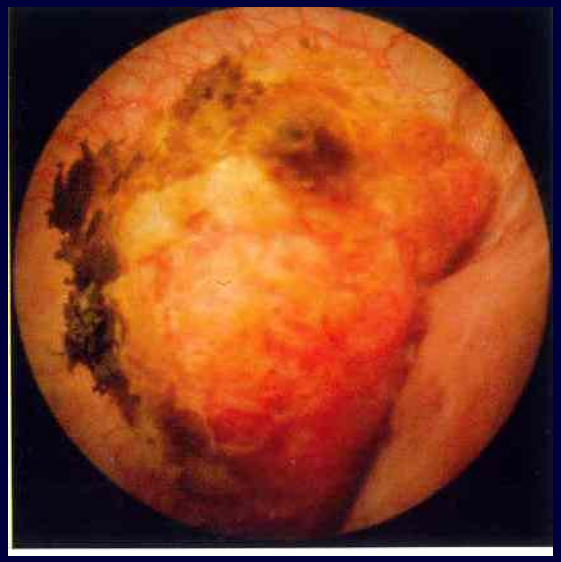
Urol Clin N Am 32 (2005) 133–145

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: • T1 tumour • G3 (high grade) tumour • CIS • Multiple and recurrent and large (> 3 cm) Ta G1G2 tumours (all conditions must be presented in this point)

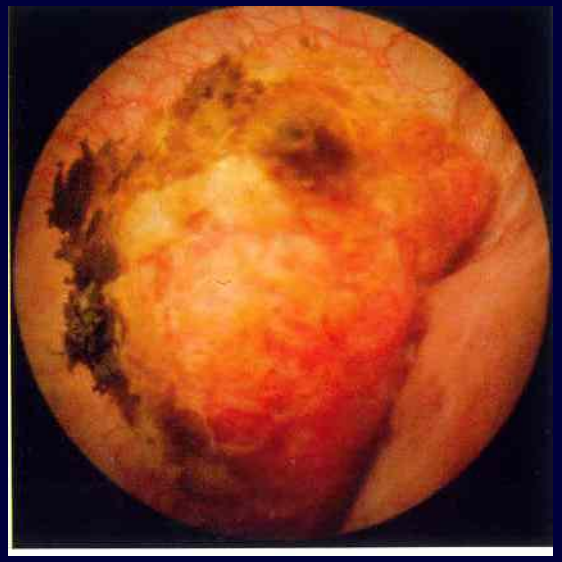
EAU Guidelines

Αντιμετώπιση T1GIII



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

Αρχική TUR



«Ιδανική»TUR σε τρία παρασκευάσματα:

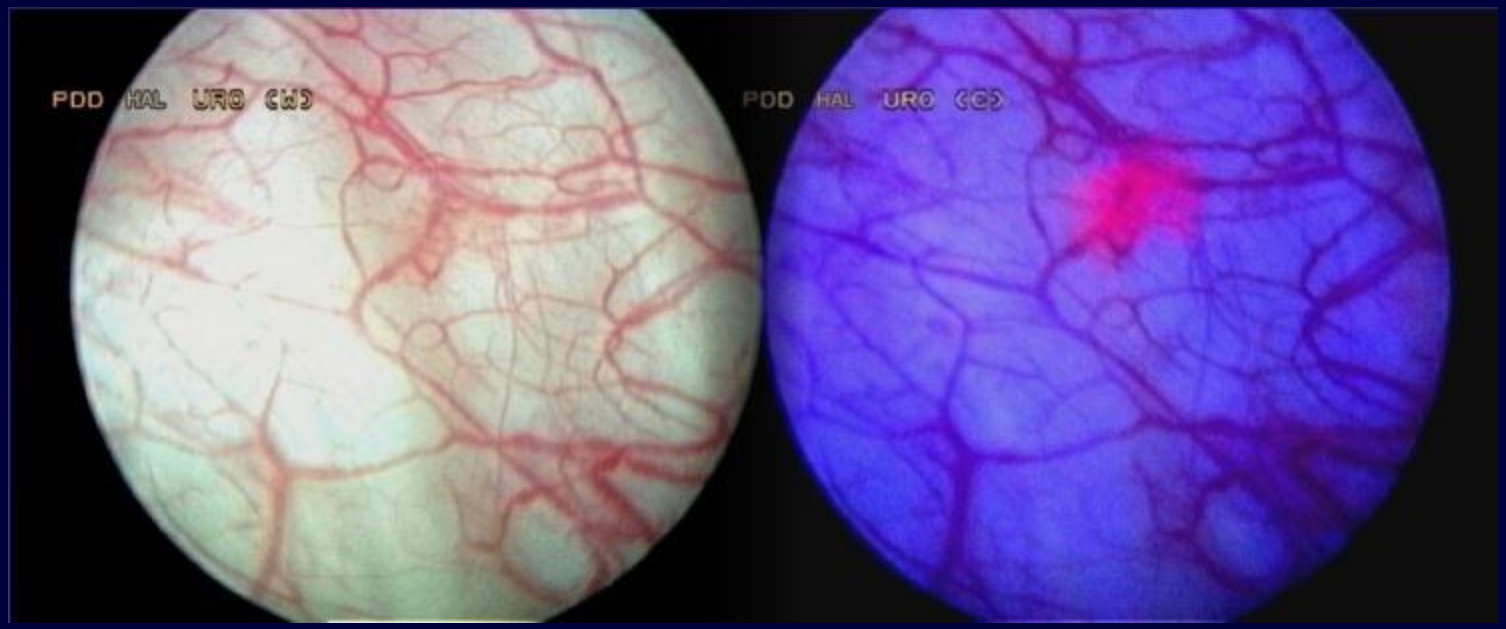
- Εξωφυτικός όγκος
- Βάση όγκου + μυικός χιτώνας
- Όρια όγκου

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

EAU Guidelines

Optimizing TUR BT
Φωτοδυναμική Διάγνωση (PDD)

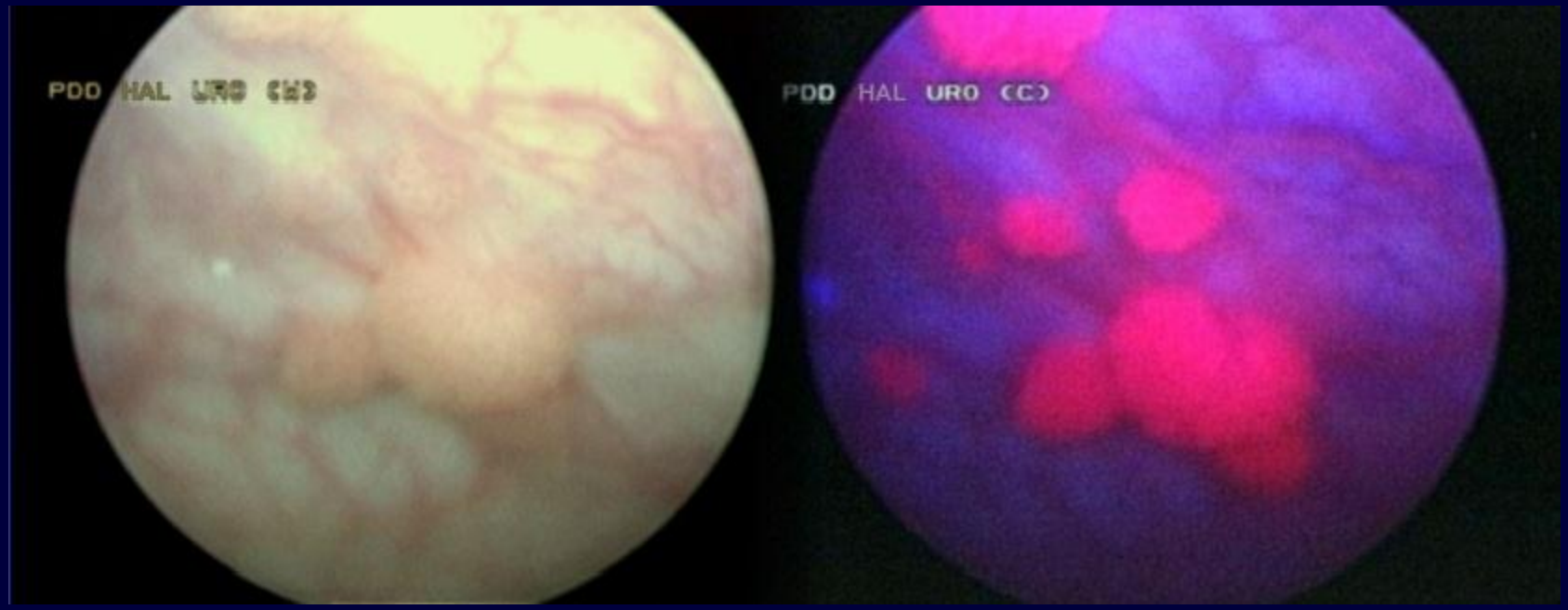
Small Papillary Tumor



Zaak, Munik 2002

Optimizing TUR BT
Φωτοδυναμική Διάγνωση (PDD)

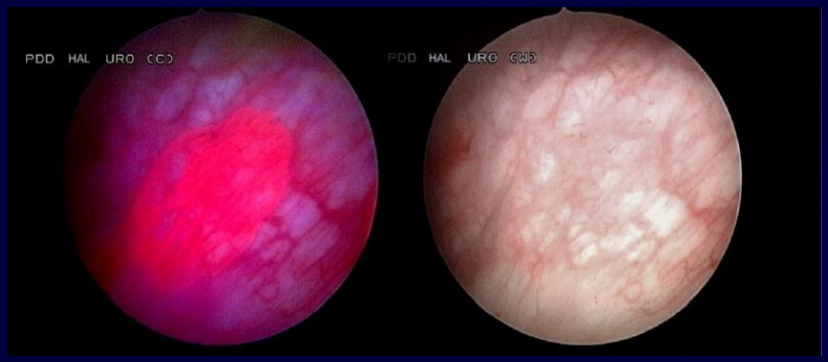
Larger multifocal papillary tumors



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

PD11-02: **En bloc resection of bladder tumours (ERBT): multivariable analysis for prediction of recurrence at mid-term follow-up**

Rodolfo Hurle*, Massimo Lazzeri, NicolòMaria Buffi, Giovanni Lughezzani, Paolo Casale, Girolamo Fiorini, Roberto Peschechera, Luisa Pasini, Silvia Zandegiacomo, Piergiuseppe Colombo, Emanuela Morenghi, Giorgio Guazzoni, Milan, Italy

D11-03: **En bloc thulium laser resection of bladder tumors: 3-yr single centre experience.**

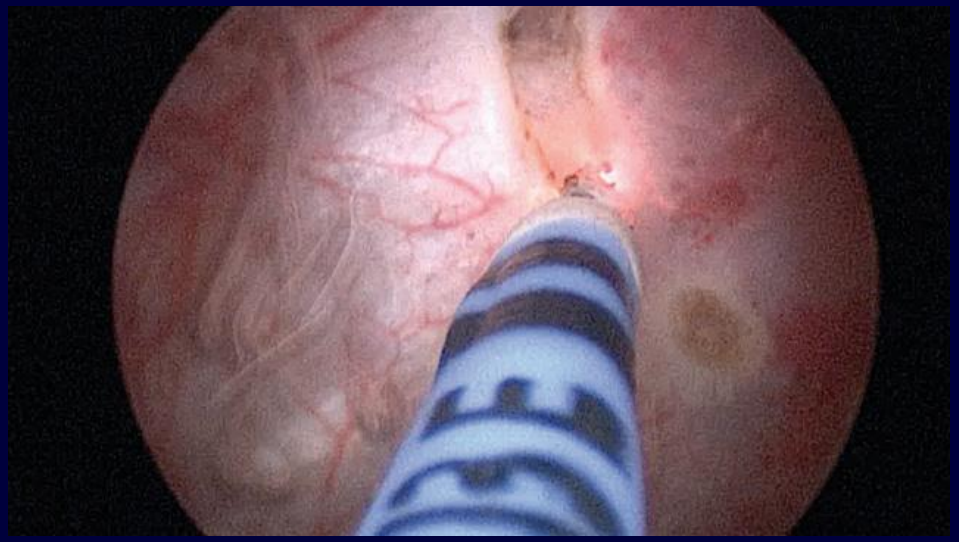
Giuseppe Simone, Rome, Italy, Alessandro Giacobbe, Turin, Italy, Rocco Papalia, Rome, Italy, Devis Collura, Leonardo D' Urso, Emanuele Castelli, Gianluca Muto, Turin, Italy, Riccardo Mastroianni, Mariaconsiglia Ferriero, Francesco Minisola, Leonardo Misuraca, Gabriele Tuderti*, Michele Gallucci, Giovanni Muto, Rome, Italy

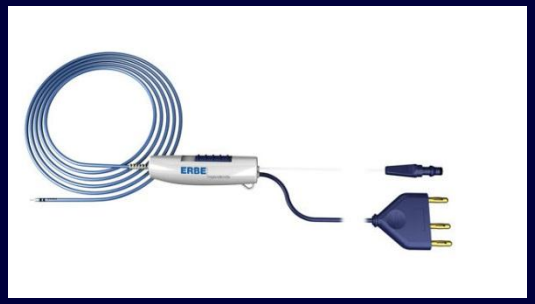
D11-04: **Transurethral Endoscopic Submucosal En blot dissection for non-muscle invasive bladder tumor: A prospective comparison study of Hybridknife assisted versus conventional dissection technique**

Yongyi Cheng*, Wexing Qu, Yi Sun, Jing Li, Liang Liang, Xi’an, China, People's Republic of

D11-04: Transurethral Endoscopic Submucosal En blot dissection for non-muscle invasive bladder tumor: A prospective comparison study of Hybridknife assisted versus conventional dissection technique

Yongyi Cheng*, Wexing Qu, Yi Sun, Jing Li, Liang Liang, Xi'an, China, People's Republic of





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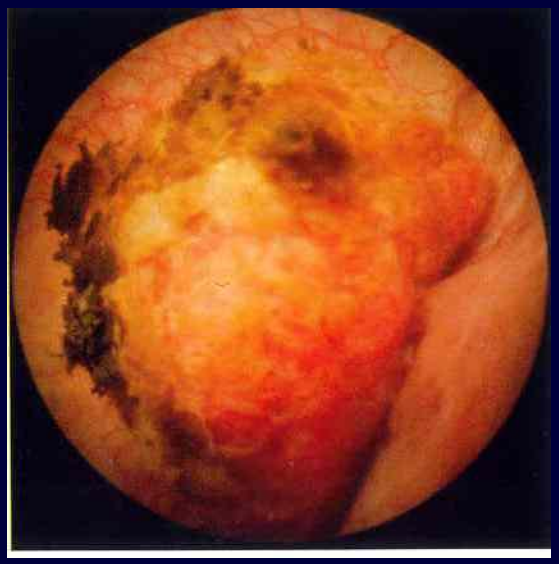
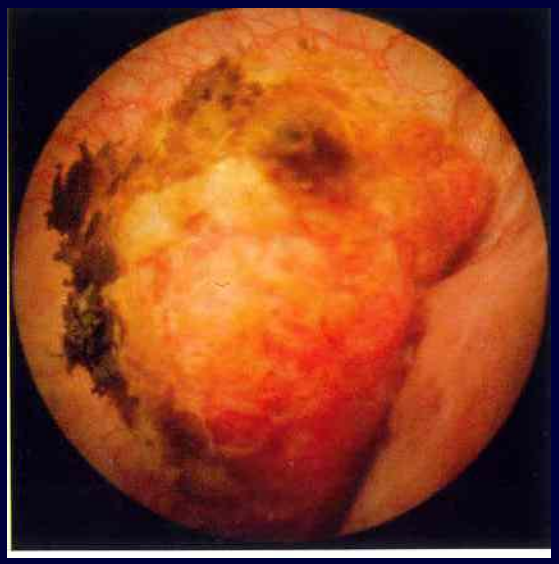
Άμεση μετ/κή ένδοκυστική ΧΜΘ



- 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

EAU Guidelines

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

EAU Guidelines

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

EUROPEAN UROLOGY 69 (2016) 231–244

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 ≥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 ≤ T2**
- **Re TUR within 2-6 weeks**
- **Only 24% were free of Tumor with 1st 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^{ο} τρίμηνο και θα χαρακτηρισθεί ως BCG refractory όγκος με εντελώς διαφορετική προγνωστική σημασία**

Ιδία παρατήρηση

Re-TUR BT

A second TURB is recommended in the following situations:	A
- after incomplete initial TURB; - if there is no muscle in the specimen after initial resection, with exception of Ta G1 tumours and primary CIS; - in all T1 tumours; - in all G3 tumours, except primary CIS.	
A second TURB should be performed 2-6 weeks after initial resection.	C

ΤυχαίεςBx/ 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

EAU Guidelines

MP13-02: **Is re-resection necessary? Re-resection of non-muscle invasive bladder cancer at a tertiary care center**

Rano Matta*, Ashraf Al Matar, Bimal Bhindi, Alexander Zlotta, Neil Fleshner, Michael Jewett, Robert Hamilton, Antonio Finelli, Girish Kulkarni, Toronto, Canada **Abstract: MP13-02**

Methods

We retrospectively identified 358 consecutive patients with pT1 high grade urothelial carcinoma of the bladder who were treated at the University Health Network, Toronto, from 2000 to 2012.

Results

The median age of the cohort was 68.9 years (18-97) with a mean follow up 3.3 years (0.08-13.3 years). Re-TUR was performed in 109 patients (40. %). The average re-TUR rate increased after 2008 from 31.6% to 51.3% (p=0.038). There was residual tumor in 70% of re-TUR cases Upstaging to T2 disease on re-TUR was seen in 16.5% of patients. There was residual pT1 in 29.4% of cases. Residual T1 disease at re-TUR was a significant risk factor for progression (HR 38.1; CI 5.9-246.6). Re-TUR was not a significant risk factor for recurrence, progression or mortality.

Conclusions

Overall, re-TUR is an important therapy, decision-making and prognostication tool in NMIBC. However, in terms of the effectiveness of re-TUR on recurrence and progression, further prospective studies will provide more definitive information.

AUA 2016

Πρόγνωση

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

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

EUROPEAN UROLOGY 49 (2006) 466–477

available at www.sciencedirect.com
journal homepage: 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[a,*], *Adrian P.M. van der Meijden*[b], *Willem Oosterlinck*[c], *J. Alfred Witjes*[d], *Christian Bouffioux*[e], *Louis Denis*[f,1], *Donald W.W. Newling*[g,2], *Karlheinz Kurth*[h,3]

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

Progression score		Prob progression 1 year (95% CI)	Prob progression 5 years (95% CI)
0	**Low**	0.2% (0%, 0.7%)	0.8% (0%, 1.7%)
2–6	**Interm.**	1.0% (.4%, 1.6%)	6% (5%, 8%)
7–13		5% (4%, 7%)	17% (14%, 20%)
14–23	**High**	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	
60–70	1	
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

EUROPEAN UROLOGY 53 (2008) 992–1002

available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

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*

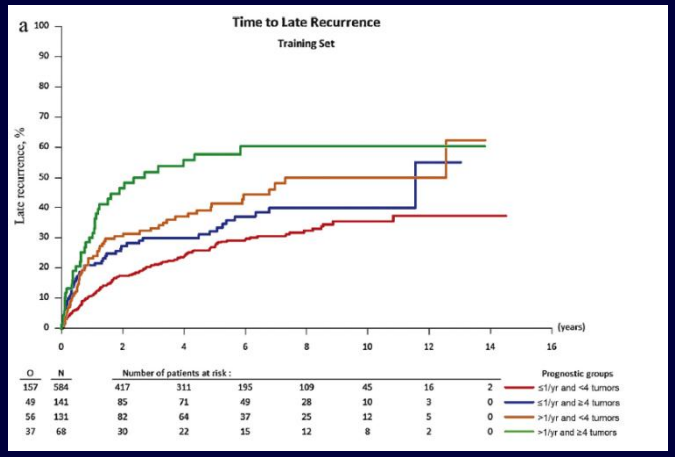
	% 1 Yr (95% CI)		% 2 Yrs (95% CI)		% 5 Yrs (95% CI)	
Score	Recurrence	Progression	Recurrence	Progression	Recurrence	Progression
0–4	8.24 (5.91–10.57)	1.17 (0.15–2.19)	12.6 (9.76–15.44)	2.16 (0.77–3.55)	20.98 (17.33–24.63)	3.76 (1.9–5.62)
5–6	12.07 (7.95–16.19)	3 (0.82–5.18)	22.28 (16.93–27.63)	4.97 (2.34–7.6)	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)

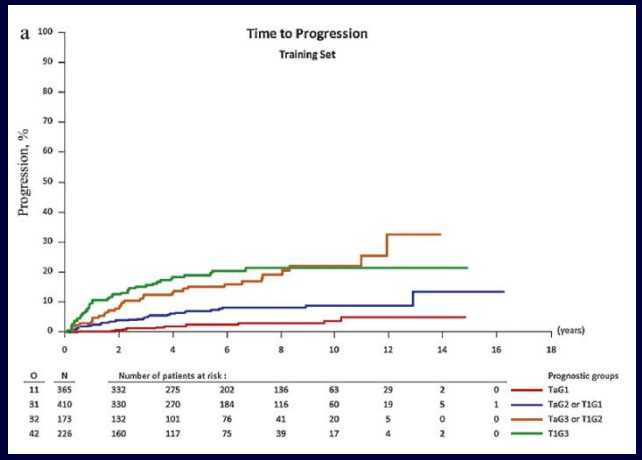
EORTC Nomograms and Risk Groups for Predicting Recurrence, Progression, and Disease-specific and Overall Survival in Non–Muscle-invasive Stage Ta–T1 Urothelial Bladder Cancer Patients Treated with 1–3 Years of Maintenance Bacillus Calmette-Guérin

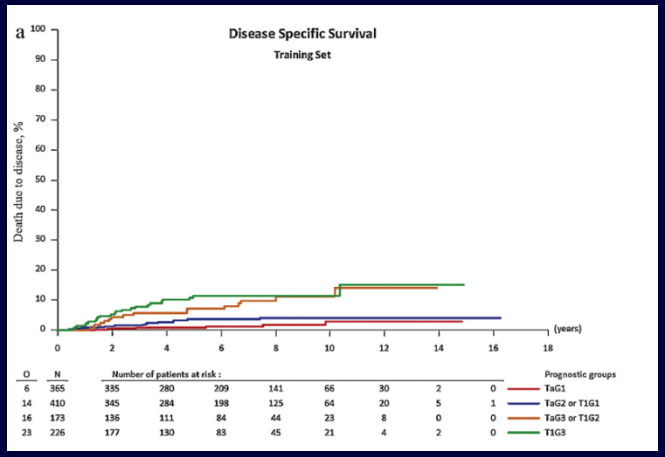
Samantha Cambier[a,†], *Richard J. Sylvester*[a,*], *Laurence Collette*[a], *Paolo Gontero*[b], *Maurizio A. Brausi*[c], *George van Andel*[d], *Wim J. Kirkels*[e], *Fernando Calais Da Silva*[f], *Willem Oosterlinck*[g], *Stephen Prescott*[h], *Ziya Kirkali*[i,‡], *Philip H. Powell*[j], *Theo M. de Reijke*[k], *Levent Turkeri*[l], *Sandra Collette*[a], *Jorg Oddens*[m]

EUROPEAN UROLOGY 69 (2016) 60–69

EORTC Nomograms and Risk Groups for Predicting Recurrence, Progression, and Disease-specific and Overall Survival in Non–Muscle-invasive Stage Ta–T1 Urothelial Bladder Cancer Patients Treated with 1–3 Years of Maintenance Bacillus Calmette-Guérin







Conclusions

NMIBC patients treated with 1–3 yr of maintenance BCG have a **heterogeneous prognosis for both time to first recurrence (according to the prior recurrence rate and number of tumors) and time to progression and death due to BCa** (based on tumor stage and grade). Patients **at high risk of recurrence and/or progression still do poorly on current maintenance schedules. Alternative treatments are urgently required**

T1 disease

or

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

or

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

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

  Mitotic activity index/mean area of 10 largest nucleii, 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-γ

- **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**

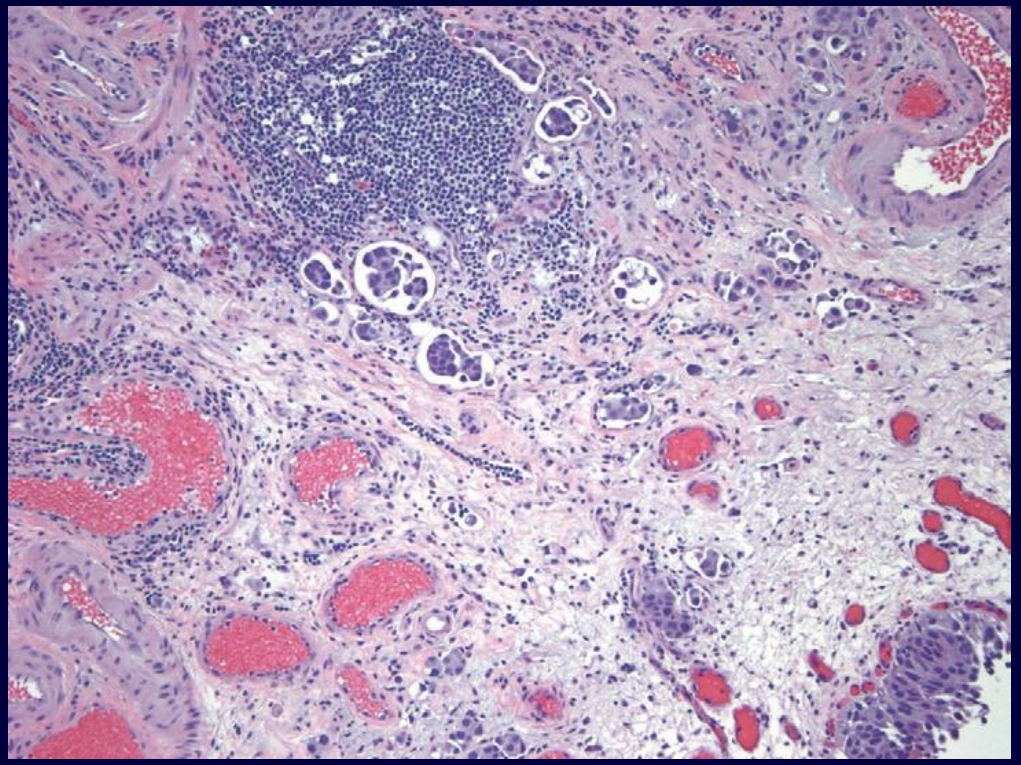
- **Για την ώρα δεν υπάρχει κάποιος δείκτης ικανός να καθορίσει τη θεραπευτική απόφαση**

UROLOGY 66 (Suppl 6A): 64–74, 2005

T1HG - Early cystectomy

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

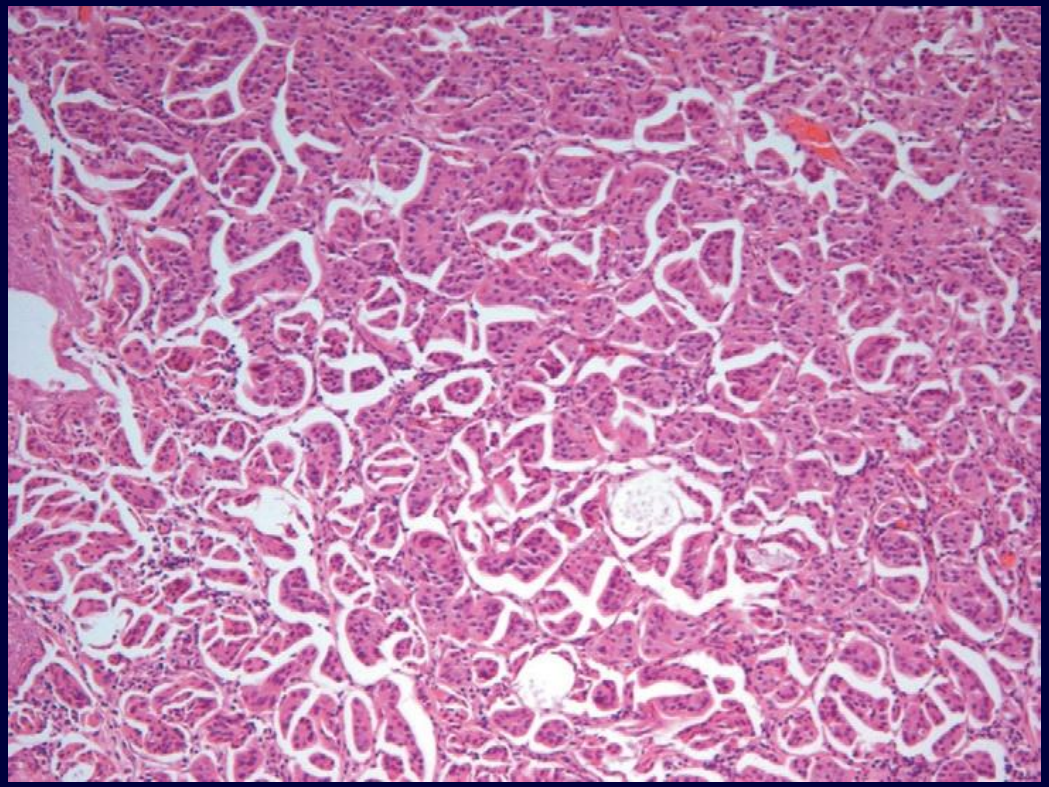
Cheryl T Lee et al. **AUA 2005:** Abstract # **911**



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**

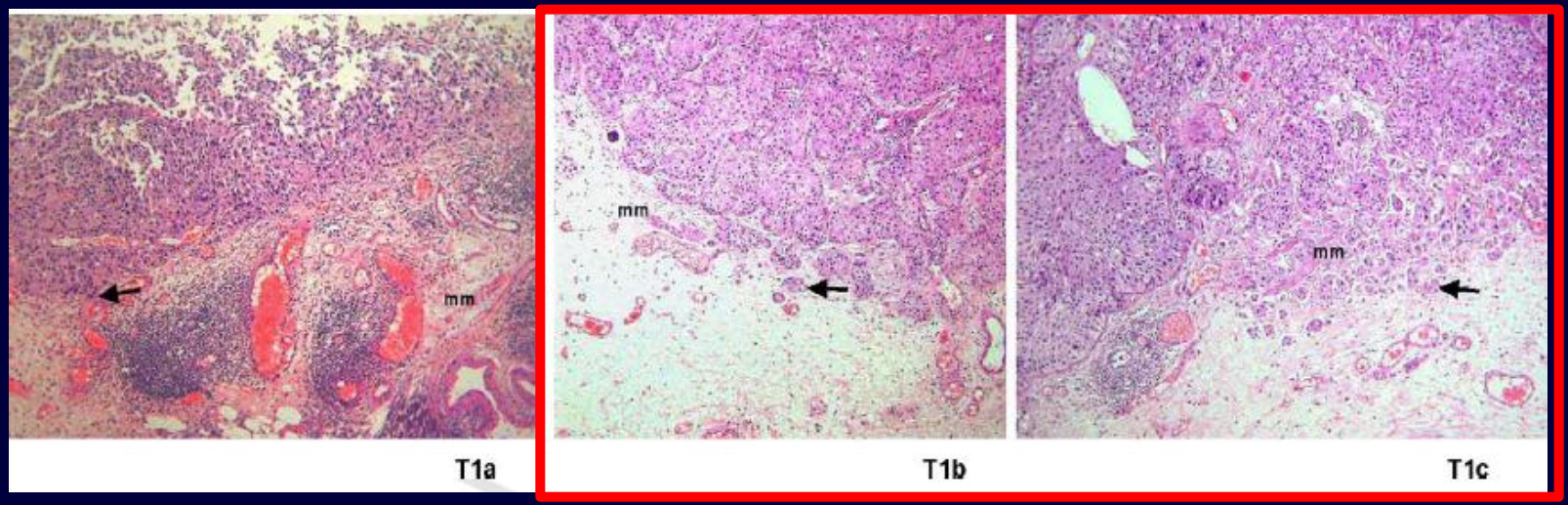


T1HG-Early cystectomy

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[a,*], I. Trias[b], C.X. Raventós[a,1], I. Español[b], L. Cecchini[a,1], S. Búcar[a], D. Salinas[a], I. Orsola[a]

[a]*Urology Department, Clínica Plató, Plato 2, 08006, Barcelona, Spain*
[b]*Pathology Department, Clínica Plató, Barcelona, Spain*



European Urology (2005)

T1b-c HG- Early cystectomy

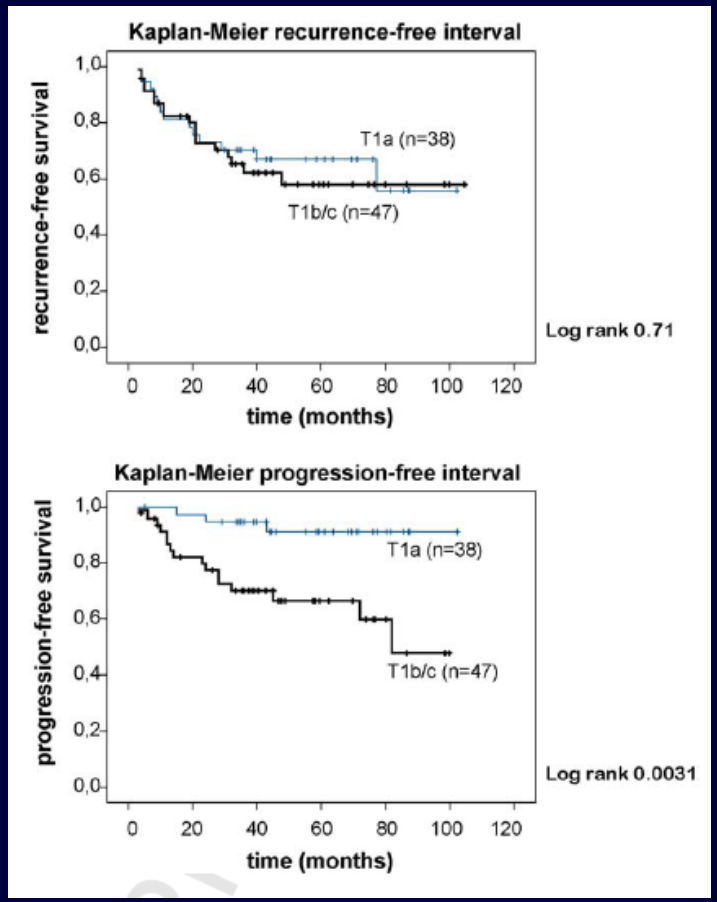
Year	Author	Staging system	Number of cases	Progression (%)	Survival (%)
1990	Younes et al. [6]	T1a (lamina propria)	15	NA	75
		T1b (into MM)	3		
		T1c (across MM)	14		11
1994	Hasui et al. [8]	T1a (Younes T1a)	60[a]	6.7	95
		T1b (Younes T1b and c)	28[a]	53.5	82
1995	Angulo et al. [21]	T1a (Younes T1a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

NA: not available.
[a] Includes grades 1, 2 and 3.
[b] Includes grades 2 and 3.
[c] T1b with CIS had risk of progression increased by a factor of 7.5.

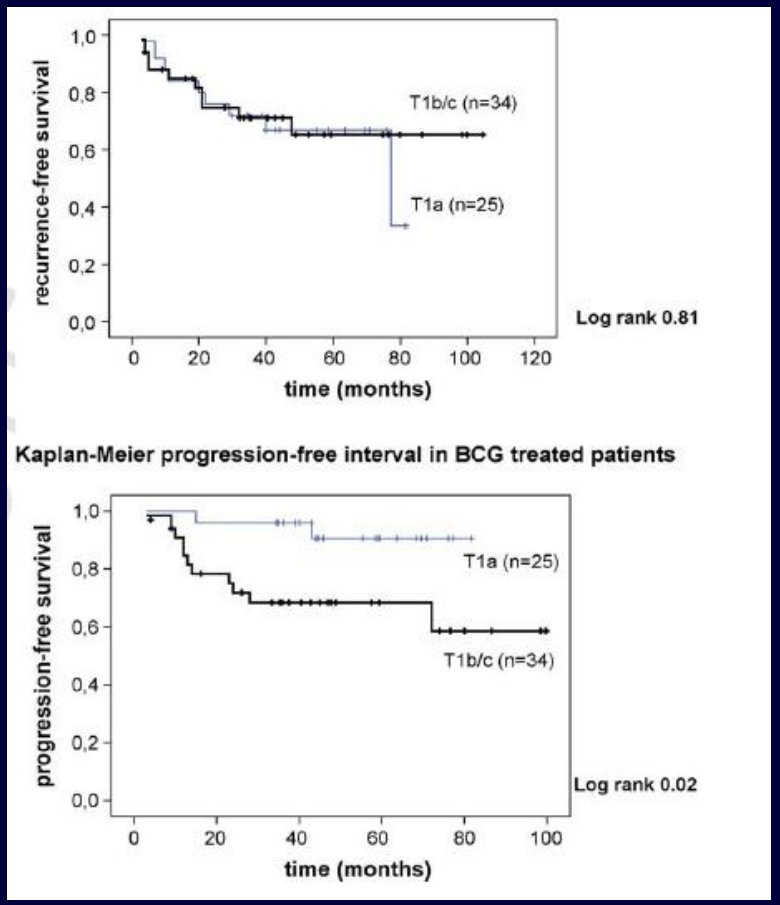
A Osola et al. European Urology (2005)

T1b-c HG-Early cystectomy

All pts

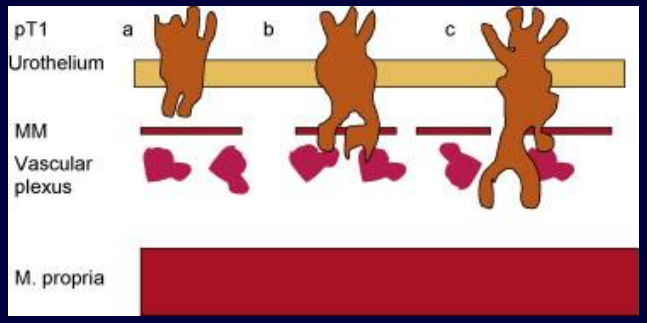


BCG treated pts



A Osola et al. European Urology (2005)

Υποσταδιοποίηση pT1

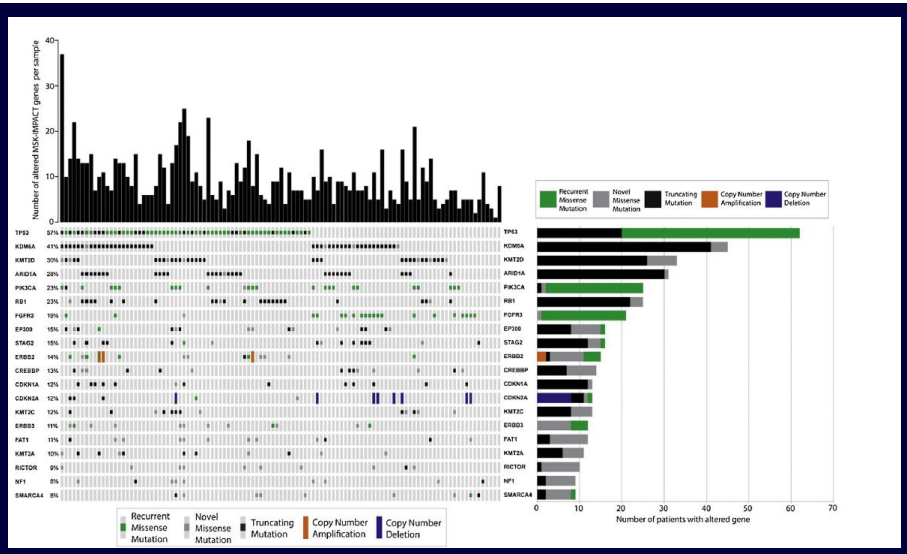


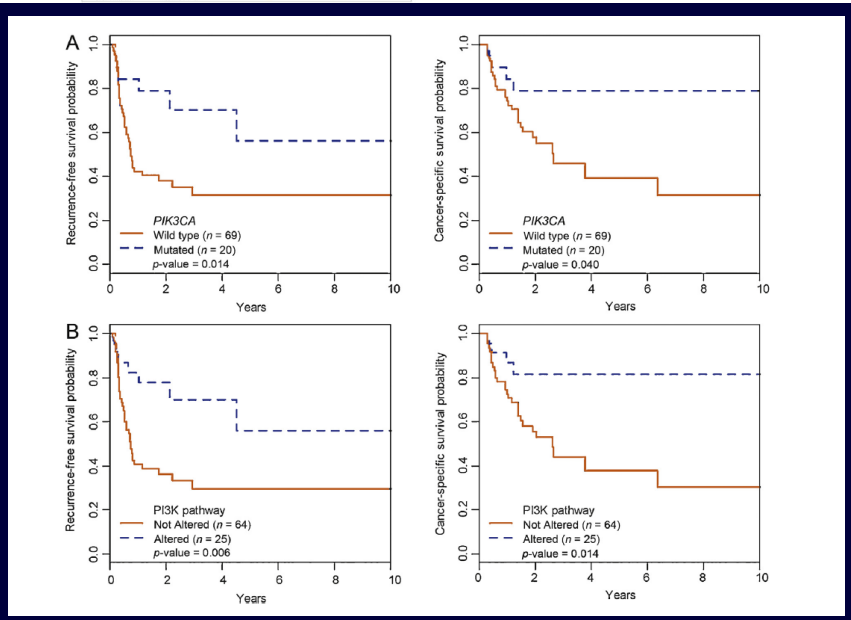
- Δεν είναι εφικτή στο 35% των περιπτώσεων
- Έχει προταθεί εναλλακτικά η μέτρηση του βάθους διήθησης του χορίου με όριο το 1,5 mm

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

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

Genomic Predictors of Survival in Patients with High-grade Urothelial Carcinoma of the Bladder





- Mutations were detected in 240 genes, with 23 genes mutated in > 5% of cases
- The presence of a recurrent phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha **(PIK3CA)** mutation was associated with improved recurrence-free survival (RFS) (hazard ratio [HR]:0.35; p = 0.014) and improved cancer-specific survival (CSS) (HR: 0.35; p = 0.040) in RC pts
- Cyclin-dependent kinase inhibitor 2A **(CDKN2A)** –altered tumors experienced worse RFS (HR: 5.76; p < 0.001) and worse CSS (HR: 2.94; p = 0.029) in multivariable analyses.

Philip H. Kim et al . Eur Urol. 67; 2015, 198-201

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

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

Table 4 – Univariable and multivariable analyses of time to recurrence

	Univariable		Multivariable	
Factor	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Age, yr				NS
<70, ≥70	1.12 (1.00–1.25)	0.047		
Sex				NS
Male, female	1.07 (0.93–1.24)	0.32		
Tumor status				NS
Primary, recurrent	1.02 (0.85–1.22)	0.82		
No. of tumors				
Single, multiple	1.38 (1.23–1.56)	<0.001	1.28 (1.12–1.47)	<0.001
Tumor size, cm				
<3, ≥3	1.37 (1.19–1.58)	<0.001	1.33 (1.15–1.53)	<0.001
Concomitant CIS				NS
No, yes	1.24 (1.09–1.40)	0.001		
Maintenance BCG				
No, yes	0.60 (0.53–0.67)	<0.001	0.61 (0.53–0.70)	<0.001

BCG = bacillus Calmette-Guérin; CI = confidence interval; CIS = carcinoma in situ; HR = hazard ratio; NS = excluded from final model because not statistically significant.

Paolo Gontero et al. Eur Urol. 67 ; 2015,74-82

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

Table 5 – Univariable and multivariable analyses of time to progression

	Univariate		Multivariate	
Factor	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Age, yr				
<70, ≥70	1.44 (1.20–1.73)	<0.001	1.36 (1.11–1.67)	0.003
Sex				NS
Male, female	1.31 (1.05–1.64)	0.015		
Tumor status				NS
Primary, recurrent	1.15 (0.87–1.53)	0.32		
No. of tumors				NS
Single, multiple	1.04 (0.86–1.26)	0.66		
Tumor size, cm				
<3, ≥3	1.91 (1.55–2.34)	<0.001	1.85 (1.51–2.28)	<0.001
Concomitant CIS				
No, yes	1.41 (1.16–1.71)	0.001	1.46 (1.17–1.82)	0.001
Maintenance BCG				
No, yes	0.78 (0.64–0.94)	0.01	0.73 (0.59–0.90)	0.004

BCG = bacillus Calmette-Guérin; CI = confidence interval; CIS = carcinoma in situ; HR = hazard ratio; NS = excluded from final model because not statistically significant.

Paolo Gontero et al. Eur Urol. 67 ; 2015,74-82

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

Table 6 – Univariable and multivariable analyses of duration of survival

	Univariate		Multivariate	
Factor	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Age, yr				
<70, ≥70	2.75 (2.33–3.24)	<0.001	2.45 (2.03–2.97)	<0.001
Sex				NS
Male, female	0.91 (0.74–1.13)	0.40		
Tumor status				NS
Primary, recurrent	1.46 (1.16–1.85)	0.002		
No. of tumors				NS
Single, multiple	1.04 (0.88–1.23)	0.65		
Tumor size, cm				
<3, ≥3	1.61 (1.34–1.94)	<0.001	1.52 (1.26–1.83)	<0.001
Concomitant CIS				NS
No, yes	1.08 (0.91–1.29)	0.38		
Maintenance BCG				
No, yes	0.76 (0.64–0.90)	0.001	0.74 (0.61–0.90)	0.002

BCG = bacillus Calmette-Guérin; CI = confidence interval; CIS = carcinoma in situ; HR = hazard ratio; NS = excluded from final model because not statistically significant.

Paolo Gontero et al. Eur Urol. 67 ; 2015,74-82

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

Table 7 – Univariable and multivariable analyses of duration of bladder cancer–specific survival

	Univariate		Multivariate	
Factor	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Age, yr				
<70, ≥70	2.03 (1.56–2.66)	<0.001	1.84 (1.36–2.49)	<0.001
Sex				NS
Male, female	1.10 (0.79–1.53)	0.56		
Tumor status				NS
Primary, recurrent	1.52 (1.04–2.22)	0.03		
No. of tumors				NS
Single, multiple	1.30 (0.98–1.73)	0.07		
Tumor size, cm				
<3, ≥3	2.34 (1.74–3.15)	<0.001	2.22 (1.65–2.99)	<0.001
Concomitant CIS				NS
No, yes	1.16 (0.87–1.55)	0.32		
Maintenance BCG				
No, yes	0.72 (0.54–0.96)	0.023	0.68 (0.50–0.93)	0.015

BCG = bacillus Calmette-Guérin; CI = confidence interval; CIS = carcinoma in situ; HR = hazard ratio; NS = excluded from final model because not statistically significant.

Paolo Gontero et al. Eur Urol. 67 ; 2015,74-82

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

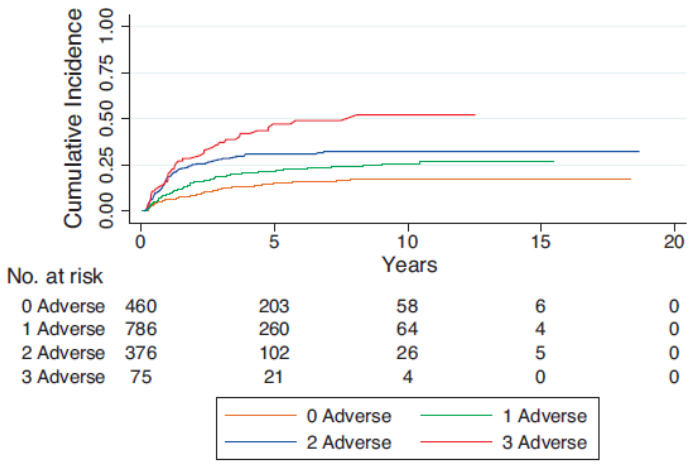


Fig. 5 – Cumulative incidence curves for time to progression according to the number of adverse prognostic factors for progression among patients ≥70 yr, tumor size ≥3 cm, and presence of carcinoma in situ.

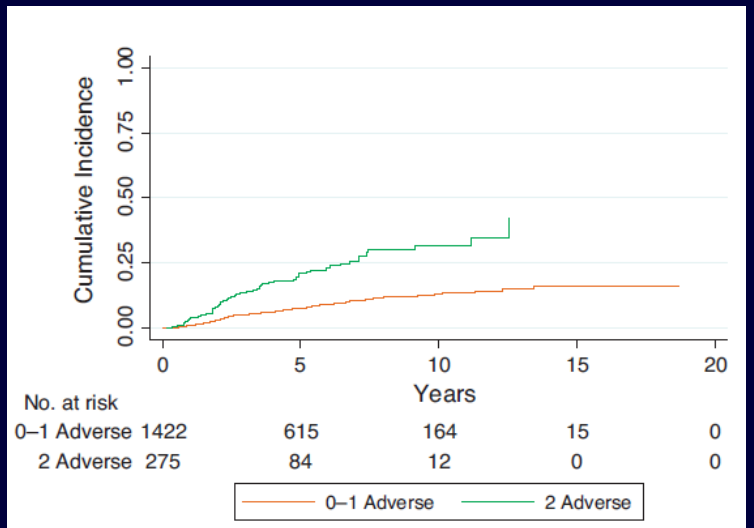


Fig. 6 – Cumulative incidence curves for bladder cancer death according to the presence of both age ≥70 yr and tumor size ≥3 cm.

Conclusions: Although the majority of T1G3 patients can be safely treated with intravesical BCG, there is a subgroup of T1G3 patients with age 70 yr, tumor size ≥ 3 cm, and concomitant CIS who have a high risk of progression and thus require aggressive treatment. T1G3 patients 70 yr with tumors 3 cm and concomitant CIS should be treated more aggressively because of the high risk of progression.

Paolo Gontero et al. Eur Urol. 67 ; 2015,74-82

MP13-12: MODERATE CHRONIC KIDNEY DISEASE (eGFR <60 ml/min) PREDICTS RECURRENCE AND PROGRESSION IN BLADDER CANCER PATIENTS TREATED WITH TRANSURETHRAL RESECTION

Michael L. Blute, Jr*, Madison, WI, Victor Kucherov, Rochester, NY, Daniel D. Shapiro, Timothy J. Rushmer, Fangfang Shi, Benjamin Fuller, Kyle A. Richards, E. Jason Abel, David F. Jarrard, Madison, WI, Edward M. Messing, Rochester, NY, Tracy M. Downs, Madison, WI

Abstract: MP13-12

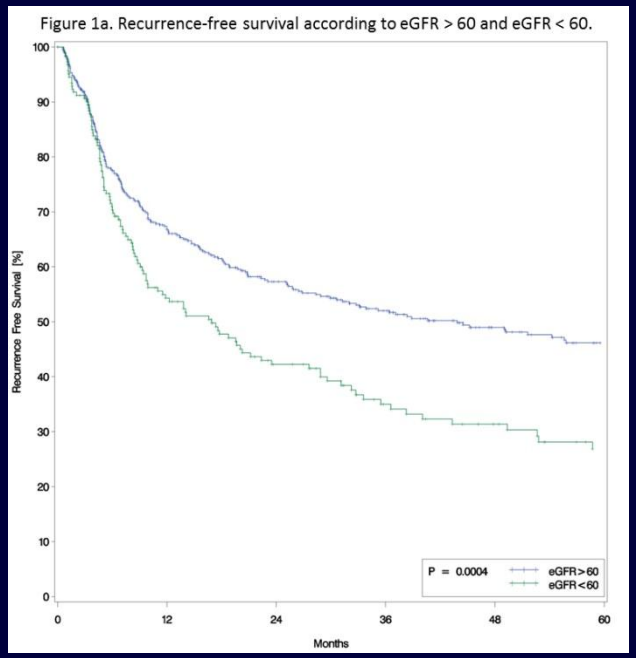
Introduction and Objectives

Chronic kidney disease (CKD) has been suggested to be associated with a higher risk of cancer development and higher cancer mortality in bladder cancer. The purpose of this study was to evaluate if moderate CKD (eGFR <60 ml/min) is associated with high rates of tumor recurrence or progression in bladder cancer patients treated with TURBT.

Methods

A multi-institutional database (University of Wisconsin, University of Rochester, NY) identified patients with serum creatinine values available prior to first TURBT for NMIBC. CKD-epidemiology collaboration formula was used to calculate estimated glomerular filtration rate (eGFR) for each patient. Cox proportional hazards models were used to evaluate associations with recurrence-free (RFS) and progression-free survival (PFS).

MP13-12: **MODERATE CHRONIC KIDNEY DISEASE (eGFR <60 ml/min) PREDICTS RECURRENCE AND PROGRESSION IN BLADDER CANCER PATIENTS TREATED WITH TRANSURETHRAL RESECTION**



Results

A total of 727 patients were identified with a median patient age of 69.8 (IQR 60.1-77.6). During a median follow-up of 3.7 (IQR 1.5-6.5) years, 400 (55%) patients had recurrence and 145 (19.9%) patients had progression of tumor stage or grade. A total of 41 (5.6%) patients had progression to muscle invasive disease (pT2). Moderate or severe CKD was identified in 183 patients according to eGFR. **Multivariate analysis identified tumor size > 3 cm (HR 1.4, 95% CI 1.1-1.8; p=0.01) and eGFR < 60 (HR 1.5, 95% CI 1.2-1.9; p=0.002) as predictors of tumor recurrence**. The 5-year RFS rate was 46% for patients with an eGFR >=60 ml/min and 27% for patients with an eGFR <60 ml/min (p-value=0.0004). Multivariate analysis also demonstrated that eGFR <60 ml/min (HR 3.7, 95% CI 1.75-7.94; p=0.001) was associated with progression to muscle-invasive disease. The 5-year PFS rate was 83% for patients with an eGFR >=60 ml/min and 71% for patients with an eGFR <60 ml/min (log rank p-value=0.01). **Subgroup analysis of patients who received BCG therapy stratified by eGFR showed that those who had CKD were more likely to experience tumor progression to muscle invasive disease (HR 7.2, 95% CI 1.93-26.50; p=0.003).**

Conclusions

Moderate CKD (eGFR<60 ml/min) at first TUR is associated with reduced RFS and PFS. Patients with reduced renal function should be considered for increased surveillance after bladder cancer diagnosis.

AUA 2016

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

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

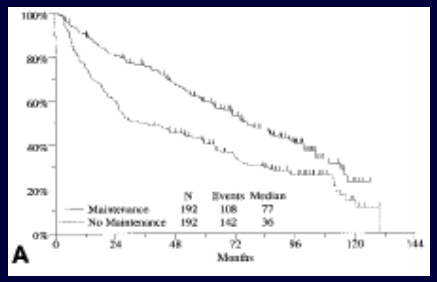
RICHARD J. SYLVESTER, et al. J Urol 2002;168:.1964-1970

- **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**

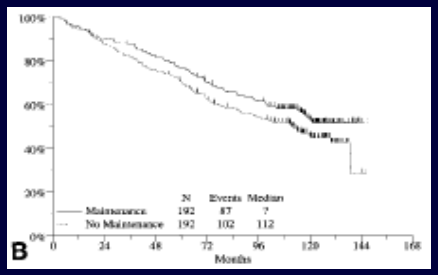
"BCG is the drug of choice for intermediate and high risk papillary tumors and the best intavesical treatment for CIS"

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

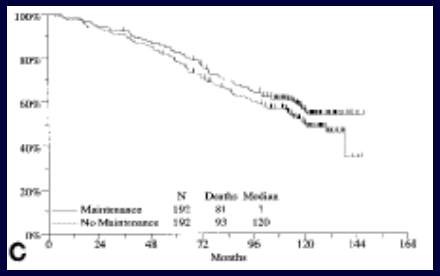
DONALD L. LAMM,et al. J Urol.2000;163: 1124-1129



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: a. Postpone the instillations b. Perform a urine culture c. Start empirical antibiotic treatment
		If symptoms persist even with antibiotic treatment: d. With positive culture: antibiotic treatment according to sensitivity. e. With negative culture: quinolones and potentially analgesic anti-inflammatory instillations once daily for 5 days (to repeat cycle if necessary) (173).
		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.

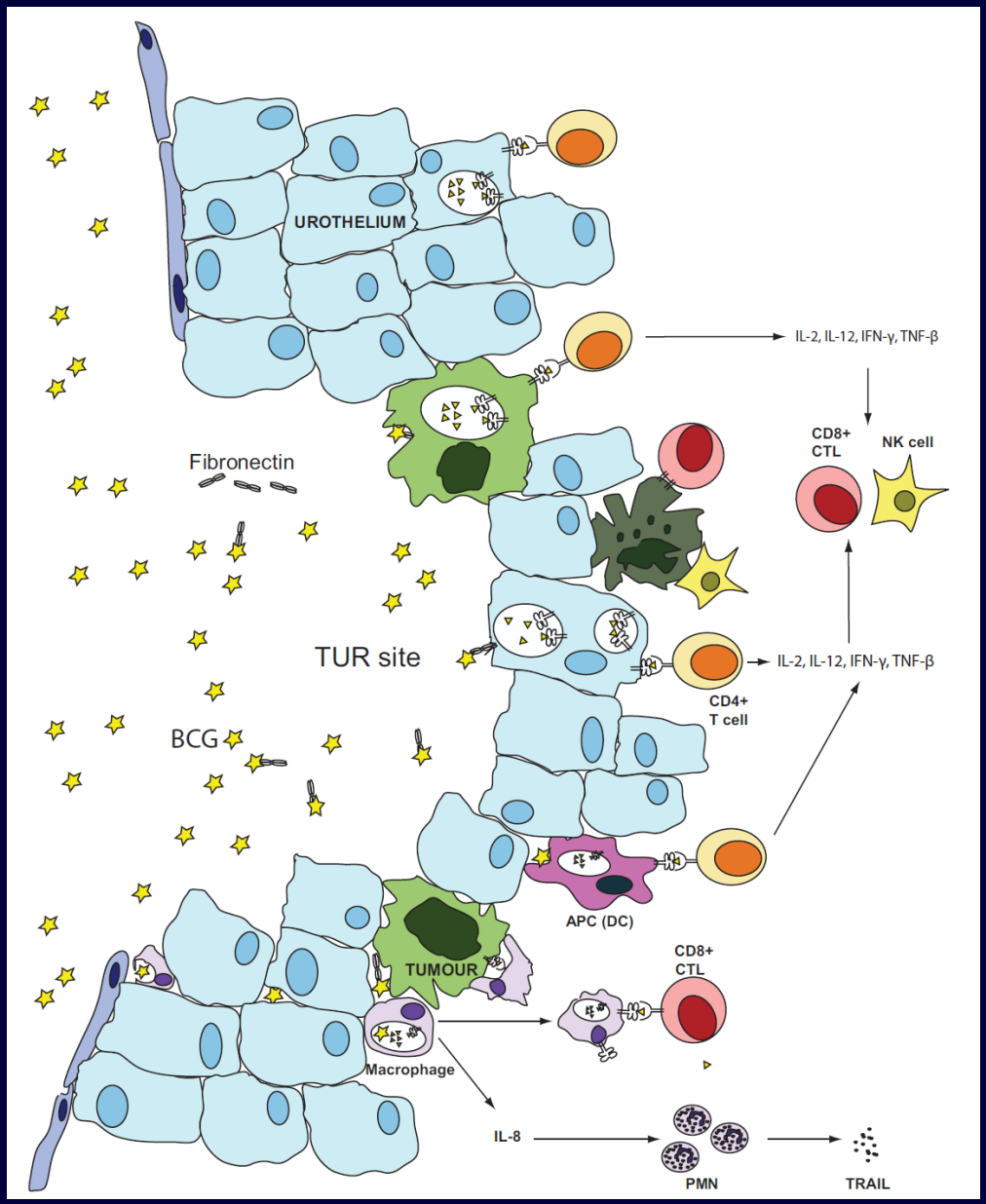
Management options for systemic side effects		
General malaise, fever		Generally resolve within 48 h, with or without antipyretics.
Arthralgia and/or arthritis		Rare complication and considered autoimmune reaction.
		Arthralgia: treatment with NSAIDs.
		Arthritis: NSAIDs and if no/partial response proceed 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: - High-dose quinolones or isoniazid, rifampicin and ethambutol 1.2 g daily for 6 months. - Early, high-dose corticosteroids as long as symptoms persist. 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.

EAU Guidelines

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)

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.

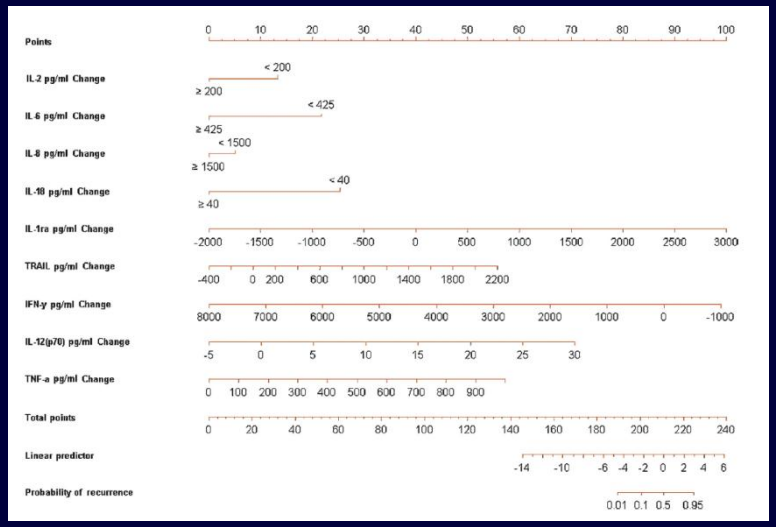
EUROPEAN UROLOGY 61 (2012) 128–145

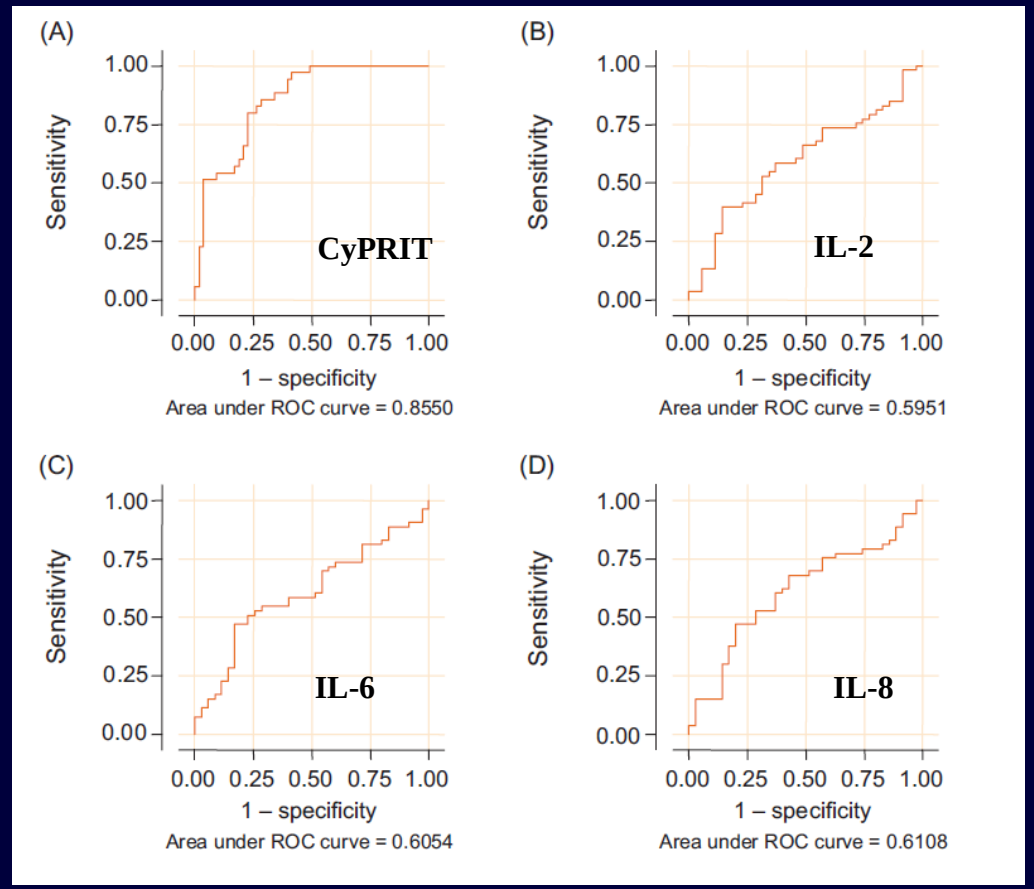
Cytokine Panel for Response to Intravesical Therapy (CyPRIT): Nomogram of Changes in Urinary Cytokine Levels Predicts Patient Response to Bacillus Calmette-Guérin

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

EUROPEAN UROLOGY 69 (2016) 197–200

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





EUROPEAN UROLOGY 69 (2016) 197–200

MP13-06: **Can intravesical administration of antifibrinolytic agent potentiate the action of Bacillus Calmette- Guerin after transurethral resection of non–muscle invasive bladder cancer? : Multicenter prospective randomized controlled study.**

Mohamed Soliman, Tanta, Egypt, Hussein Aldaqadossi*, Fayoum, Egypt, Ahmed El-Abd, Ahmed Abou- Ramadan, Mohamed El-Gharabawy, Abd-Elhamid El-Bahnasy, Tanta, Egypt, Mohamed Abd-Eltawab, Aswan, Egypt **Abstract: MP13-06**

AUA 2016

Methods

Patients in group A subjected to intravesical instillation of BCG plus 2 gm of tranexamic acid while patients in group B were subjected to intravesical instillation of BCG alone. Prothrombin time was determined at 2 hours after instillation.

Results

This study included 96 patients with mean age of 52.4 ± 6.2 .They were prospectively randomized into 2 groups (48 each). Follow-up ranged from 6 to 24 months (mean of 15.2 ± 9 months). Four patients were lost to follow up (2 in each group). Another 15 patients (8 in group A and 7 in group B) developed serious BCG complications and excluded from the study. Postoperative prothrombin time showed no significant difference between both groups (P= 0.3). In the remaining 77 patients (38 patients in group A and 39 patients in group B), **recurrence was reported in 3 out of 38 patients in group A (7.9%) and 11 out of 39 patients in group B (28%) with a statistically significant difference between both groups (P=0.036). Progression was reported in only one patient in group A (2.6%) and 8 patients in group B (20.5%) with a statistically significant difference (P=0.0286).**

Conclusions

Intravesical instillation of antifibrinolytic agents with BCG has improved the antitumor efficacy of BCG in the management of non–muscle invasive bladder cancer following TURBT. Further studies including large number of cases are required to support these findings.

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%**

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

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

EAU Guidelines

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- Cystectomy

Category	Treatment recommendation	GR
BCG refractory tumour	1. Radical cystectomy 2. Bladder-preserving strategies in patients not suitable for cystectomy	B
High-grade recurrence after BCG	1. Radical cystectomy 2. Repeat BCG course 3. Bladder-preserving strategies	C
Non-high-grade recurrence after BCG for primary intermediate-risk tumour	1. Repeat BCG or intravesical chemotherapy 2. Radical cystectomy	C

EAU Guidelines

BCG failure
Second-line intravesical therapy

2nd line BCG (response: 50%)

BCG+INF-A2b
Optimization of intavesical chemotherapy
Local microwave hyperthermia + MMC (Synergo)
Photodynamic Therapy (5-ALA)
Intravesical Gemcitabine, Docetaxel

↓

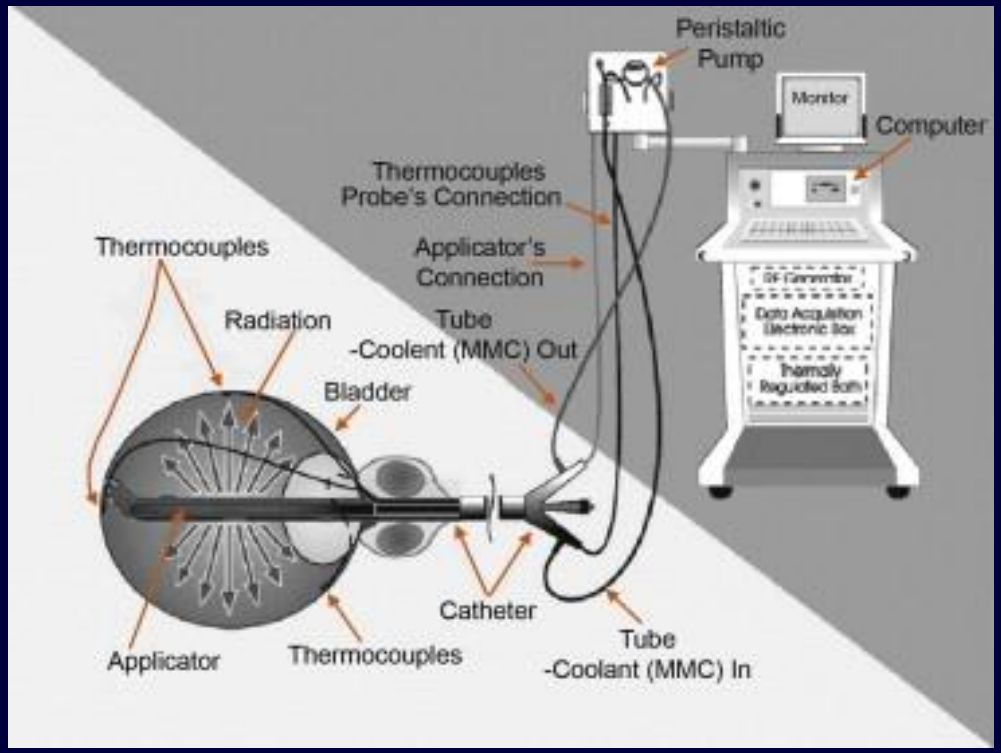
"Oncologically inferior than RC"

EAU Guidelines

BCG failure
Bladder Preservation Therapies

First author	Treatment modality (study phase)	*n*	Failures	Follow-up	NED, %	RFS, %	Rec, %	Prog, %	RC, %	Comments
Dalbagni [37]	IV gemcitabine	30	26	19 mo (range: 0–35)	50	21	40	3.5	37	Phase 2 trial
Dalbagni [38]	IV gemcitabine	18	16	12 wk	39	–	–	–	–	Phase 1 trial
Bartoletti [39]	IV gemcitabine	116	40	13.6 mo	–	–	32.5	–	–	Recurrence in 32.5% of BCG failures vs 21% BCG-naïve group; 43.7% of high-risk failures developed recurrence vs 25% of intermediate-risk failures; phase 2 study
Mohanty [40]	IV gemcitabine	35	35	18 mo	60	–	31.4	8.75	–	–
Di Lorenzo [41]	IV gemcitabine	80	80	15.5 mo (range: 6–22)	–	19	52.5	33	33	Recurrence and 2-yr DFS better for GC vs BCG ($p = 0.002$ and $p < 0.008$, respectively); phase 3 RCT
Addeo [42]	IV gemcitabine	54	46	36 mo	–	–	28	11	–	Recurrence free: 72% GC vs 61% MMC; DFS in favour of GC ($p = 0.0021$); phase 3 RCT
McKiernan [49]	IV docetaxel	18	18	12 wk	28	–	72	5.5	–	Phase 1 study
Laudano [50]	IV docetaxel	18	18	48.3 mo	22	44–61	61	5.5	33	Long-term follow-up of McKiernan [49]; median DFS, 13.3 mo
Barlow [51]	IV docetaxel	33	33	29 mo	61	32–45	39	–	–	5-yr DSS: 83%; 5-yr OS: 71%
Bassi [54]	IV paclitaxel	16	16	1 wk	60	–	40	–	–	Phase 1 study
McKiernan [55]	IV paclitaxel	18	18	6 wk	56	–	44	0	22	Phase 1 study
Joudi [36]	BCG plus interferon-α	1007	467	24 mo	45	–		–	–	Of BCG-failure group, 45% disease free vs 59% BCG naïve ($p < 0.0001$); phase 2 trial
Witjes [45]	Thermochemotherapy	51	34	27 mo	51	–	49	–	10.2	Synergo working party study
Nativ [46]	Thermochemotherapy	111	111	16 mo (range: 2–74)	–	–	56–85	3	–	2-yr recurrence rate 61% if no maintenance vs 39% for maintenance ($p = 0.01$)
Halachmi [47]	Thermochemotherapy	56	19	20 mo (range: 2–49)	67	49.3	33.3	7.9	12	KM-estimated probability of recurrence 50.7% at 2 yr for BCG-failure cohort vs 42.9
Waidelich [57]	Photodynamic therapy	24	24	36 mo (range: 12–51)	29	–	70.8	16.6	12.5	–
Berger [58]	Photodynamic therapy	31	10	23.7 mo (range: 1–73)	–	40	60	–	–	–
Breyer [56]	MMC plus gemcitabine	10	9	26 mo	60	–	40	10	0	Only 10 patients

BCG failure
Thermotherapy/Synergo



BCG failure
Thermotherapy/Synergo

First author	Treatment modality (study phase)	*n*	Failures	Follow-up	NED, %	RFS, %	Rec, %	Prog, %	RC, %	Comments
Witjes [45]	Thermochemotherapy	51	34	27 mo	51	–	49	–	10.2	Synergo working party study
Nativ [46]	Thermochemotherapy	111	111	16 mo (range: 2–74)	–	–	56–85	3	–	2-yr recurrence rate 61% if no maintenance vs 39% for maintenance ($p = 0.01$)
Halachmi [47]	Thermochemotherapy	56	19	20 mo (range: 2–49)	67	49.3	33.3	7.9	12	KM-estimated probability of recurrence 50.7% at 2 yr for BCG-failure cohort vs 42.9

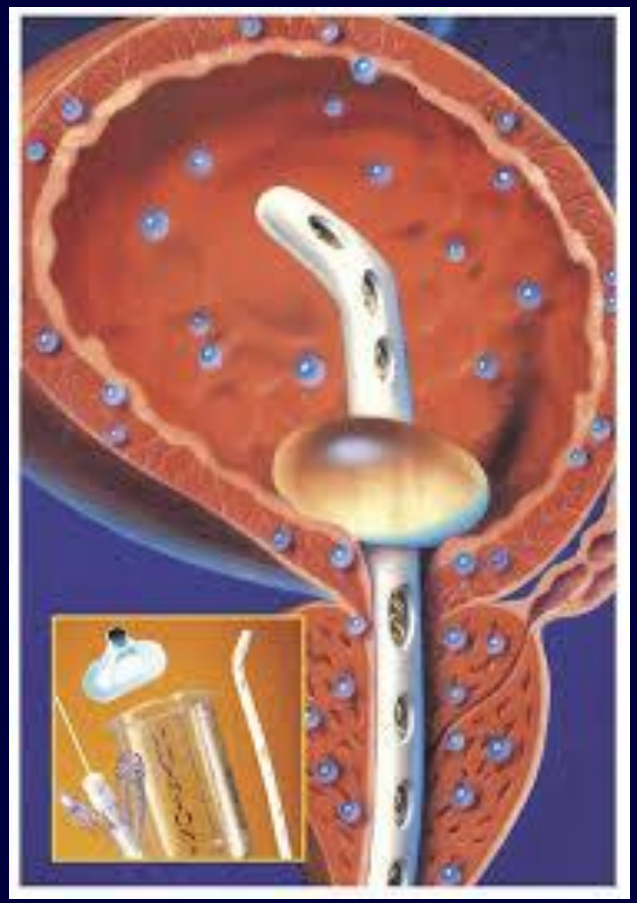
80mg MMC: TC weekly x6-8 weeks ,maintenance x4-6 sessions every 6-8 weeks

In a recent systematic review : TC 59% relative reduction in NMIBC recurrence compared with MMC alone, with a bladder preservation rate of 87.6%,

Lammers RJM, et al. Eur Urol 2011;60:81–93.

UK bladder cancer trial (HYMN, ClinicalTrials.gov identifier NCT01094964)
Phase 3 trial : TC +MMC vs. 2nd course of BCG in NMIBC with BCG failure

BCG failure
Εν δυνάμει νέες θεραπείες
EMDA MMC



BCG failure
Εν δυνάμει νέες θεραπείες
EMDA MMC

RPT: 108 high risk BCG –naïve NMIBC pts.

	EMDA MMC	MMC	BCG	p value
CR 3 months	**53%**	**28%**	**56%**	0.036
CR 6 months	**58%**	**31%**	**64%**	0.012
Time to Rec./months	**35**	**19,5**	**26**	0.013

Peak plasma concentrations of MMC:
5.5 times higher (43 ng/ml vs 8 ng/ml) in EMDA MMC

Di Stasi SM, et al. J Urol 2003;170:777–82

BCG failure
Εν δυνάμει νέες θεραπείες
Sequential BCG+EMDA MMC

RPT: 212 high risk BCG –naïve NMIBC pts./fu 88 months

	EMDA MMC+ BCG	BCG	p value
Dis.Free/months	**69**	**21**	0.00012
Rec.Rate	**42%**	**58%**	0.0012
Pogr. Rate	**9,3%**	**22%**	0.004
DSM	**5,6%**	**16,2%**	0.01
OM	**21,5%**	**32,4%**	0.045

Di Stasi SM, et al. Lancet Oncol 2006;7:43–51
Di Stasi SM, et al. World J Urol 2009;27:325–30

BCG failure
Εν δυνάμει νέες θεραπείες

Study title	Phase	Investigator	Study ID
Phase 3 randomised study of intravesical MMC and bladder hyperthermia versus intravesical BCG or standard therapy as second-line therapy in patients with recurrent NMIBC after induction or maintenance BCG	3	Cancer Research UK	HYMN; NCT01094964
Efficacy and safety evaluation of EN3348 (MCC) as compared to MMC in the intravesical treatment of subjects with BCG-recurrent/refractory NMIBC	3	Endo Pharmaceuticals	NCT01200992
Phase 1 and 2 trial of Abraxane for treatment of refractory BCa	1 + 2	Abraxis Oncology	NCT00583349
RAD0001 and intravesical gemcitabine in BCG-refractory primary or secondary carcinoma in situ of the bladder	1 + 2	Novartis Pharmaceuticals	NCT01259063
Phase 2b trial of intravesical DTA-H19/PEI in patients with intermediate-risk superficial BCa	2b	BioCancell Therapeutics	NCT00595088
Sunitinib malate in treating patients with recurrent transitional cell BCa (trial ongoing but not recruiting at present)	2	Pfizer	NCT01118351
Study of Mycobacterium w in BCG-refractory superficial transitional cell BCa (trial recently completed)	1	Cadila Pharmaceuticals	NCT00694798
Efficacy study of recombinant adenovirus for patients with resistant superficial BCa (approved but not yet active)	2 + 3	Cold Genesys Inc.	NCT01438112
Oral lenalidomide and intravesical BCG for therapy of BCa	2	University of South Florida	NCT01373294
Phase 2 study of selective bladder-preserving radiotherapy and concurrent cisplatin in patients with stage I BCa	2	National Cancer Institute	NCT00981656
Phase 1b intravesical administration of SCH721015	1b	MD Anderson Cancer Center	NCT01162785
Cis-urocanic acid in patients with primary or recurrent NMIBC	1	BioCis Pharma	NCT01458847

MP13-19: **A Phase II/III Trial of CG0070, an Oncolytic Adenovirus, for BCG-Refractory Non-Muscle-Invasive Bladder Cancer (NMIBC)**

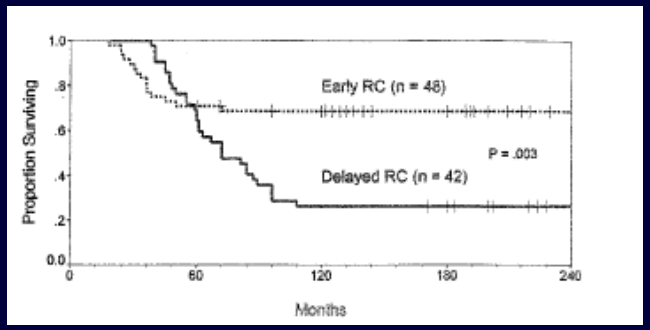
Vignesh T. Packiam*, Alexa N. Campanile, Chicago, IL, Daniel A. Barocas, Nashville, TN, Karim Chamie, Los Angeles, CA, Ronald L. Davis III, Winston-Salem, NC, A. Karim Kader, San Diego, CA, Donald L. Lamm, Pheonix, AZ, Alex W. Yeung, Santa Ana, CA, Gary D. Steinberg, Chicago, IL

MP13-20: **Second-generation antisense oligonucleotide - Hsp27 a new intravesical treatment for bladder cancer: Phase 1clinical trial.**

Sebastian Frees*, Eliana Beraldi, Kim Chi, Ladan Fazli, Peter Black, Martin Gleave, Alan So, Vancouver, Canada

T1 GIII – BCG FAILURE
Early vs. delayed cystectomy

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



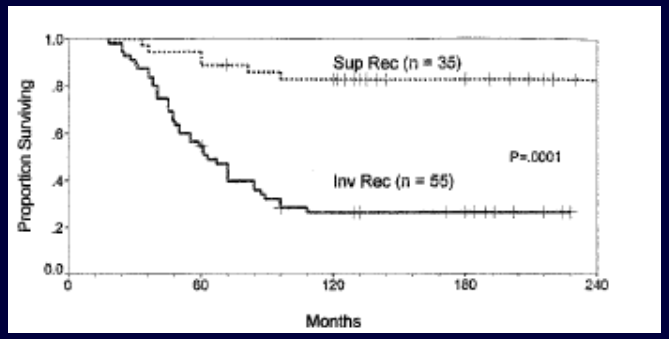
pT0: Early 33pts, Delayed 11pts

DOD: Early 15 pts, Delayed 31 pts

Vs.

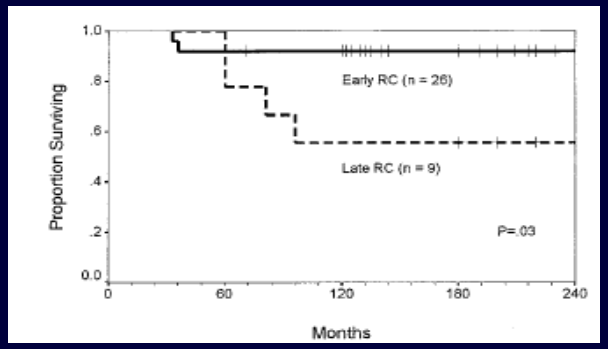
Mortality: 2,5%

Morbidity: 28%



pT0: Early 29pts, delayed 15pts

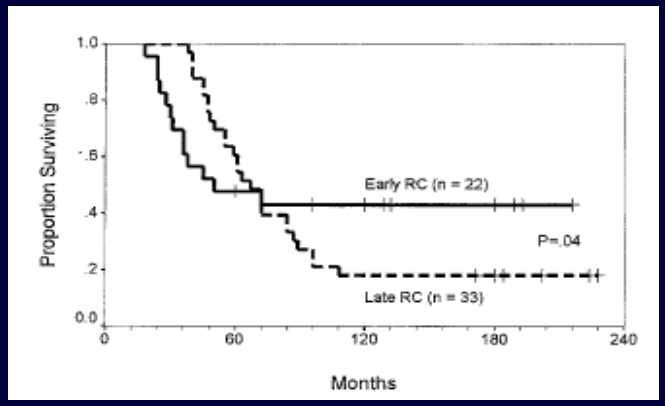
DOD: Early 6 pts, Delayed 40 pts



Recurrent SBC

pT0: Early 24pts, Delayed 5pts

DOD: Early 2 pts, Delayed 4 pts



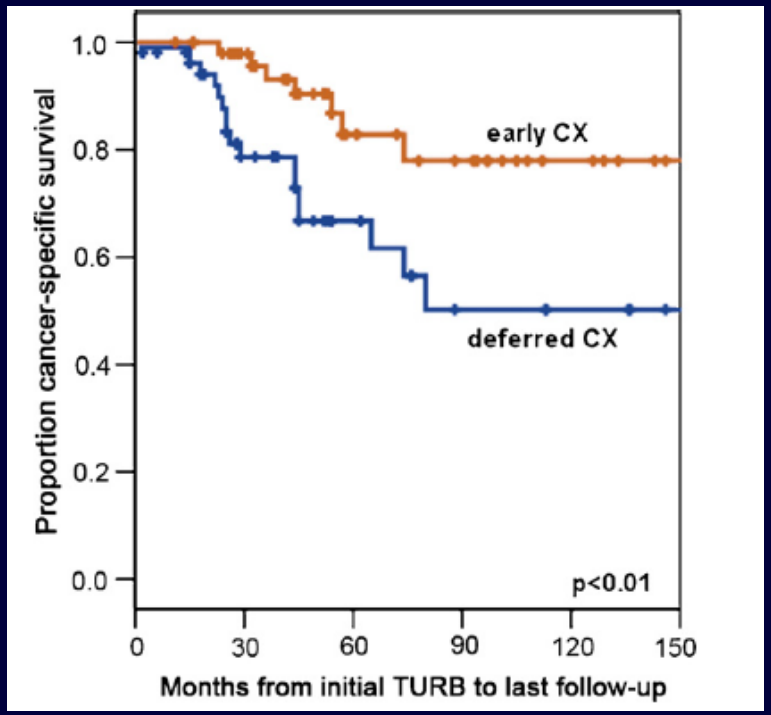
Progressed Invasive Ca

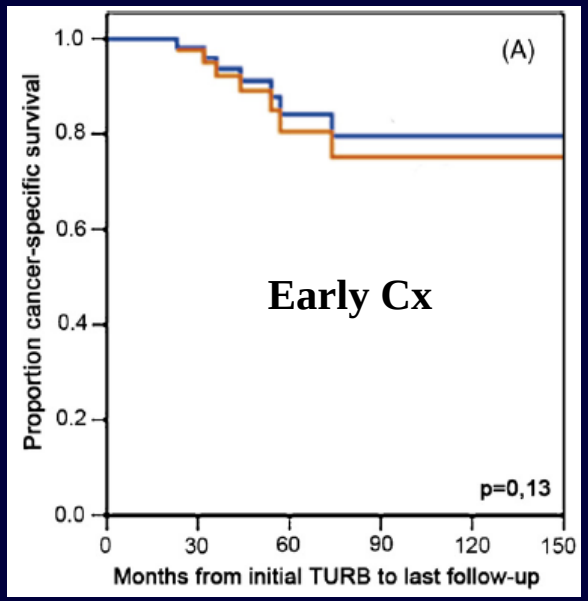
pT0: Early 9pts, Delayed 6pts

DOD: Early 13 pts, Delayed 27 pts

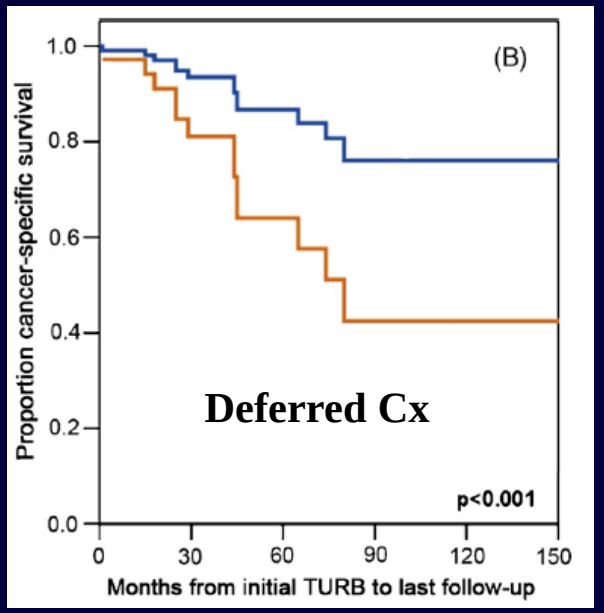
Early Versus Deferred Cystectomy for Initial High-Risk pT1G3 Urothelial Carcinoma of the Bladder: Do Risk Factors Define Feasibility of Bladder-Sparing Approach?

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





T1G3 +/- CIS



European Urology 53 (2008) 146–152

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.

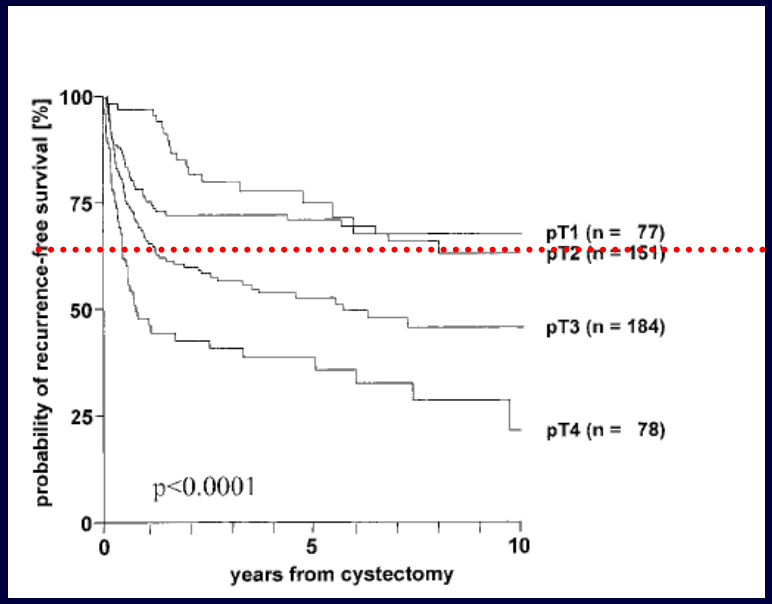
Κυστεκτομή

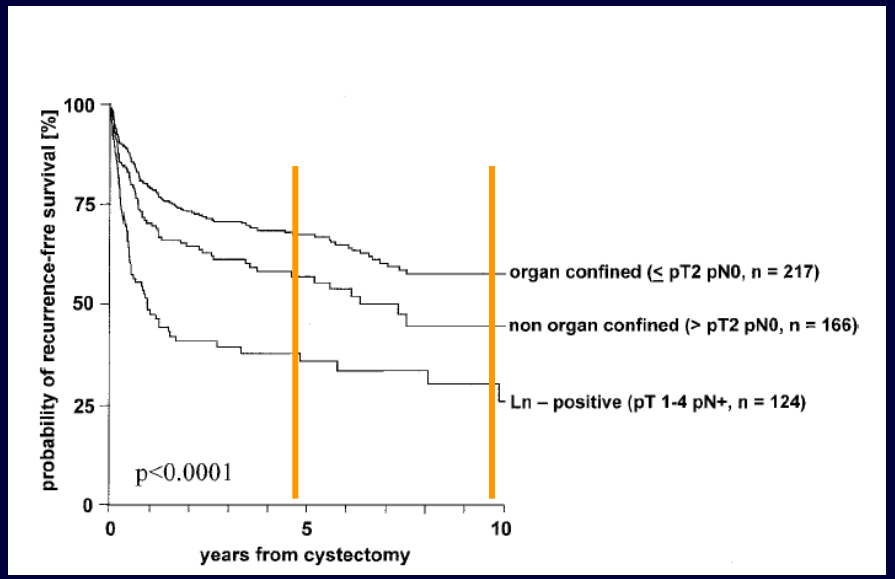
Immediate radical cystectomy may be offered to patients at highest risk of tumour progression. In patients with BCG failure, cystectomy is recommended.

(Grade of recommendation: C)

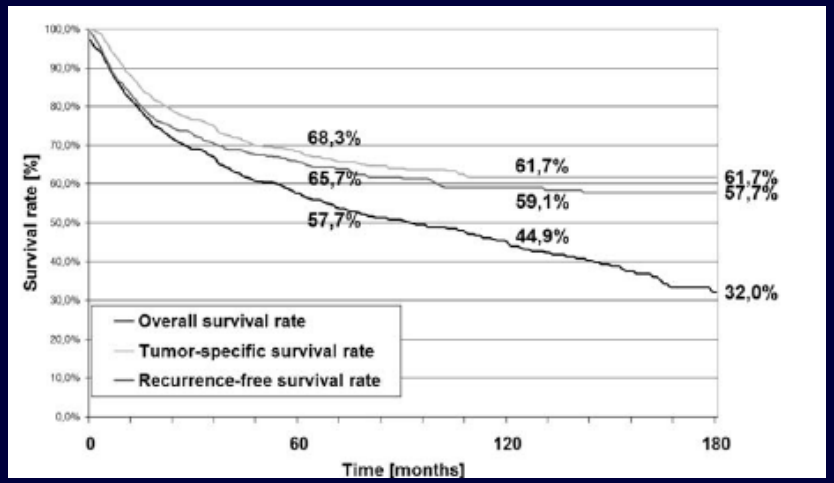
Ογκολογικό αποτέλεσμα

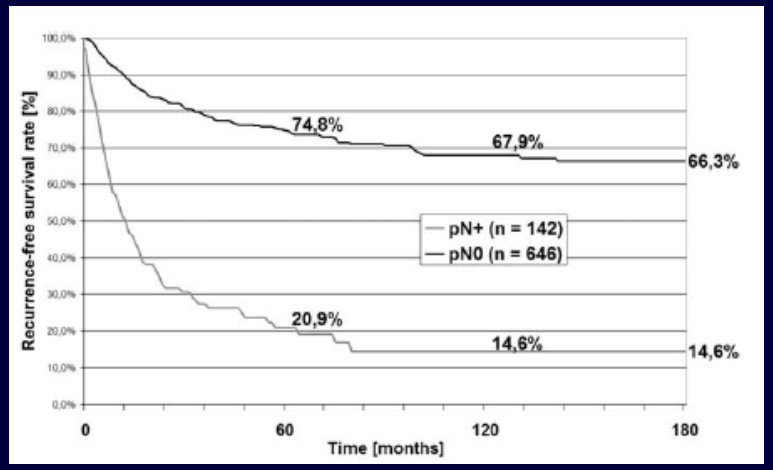
Madersbacher,Studer et al, J Clin Oncol 2003; 21:690-696





Ογκολογικό αποτέλεσμα





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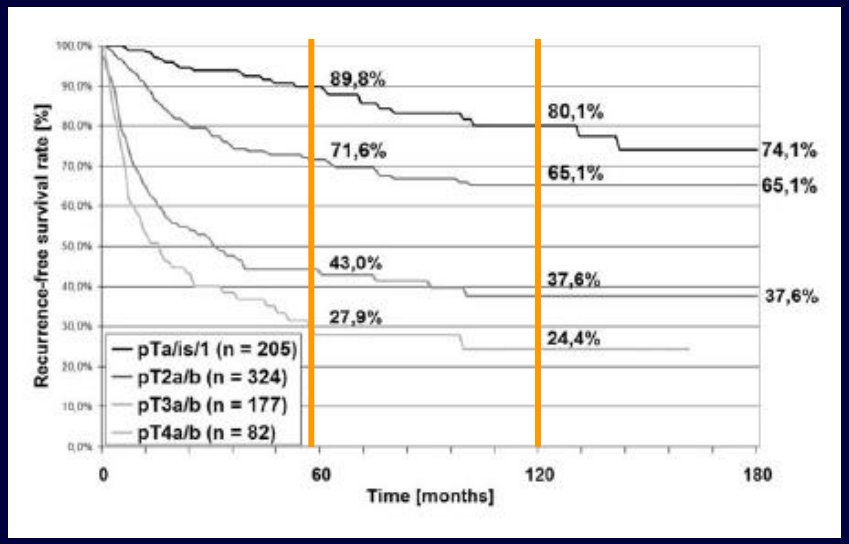

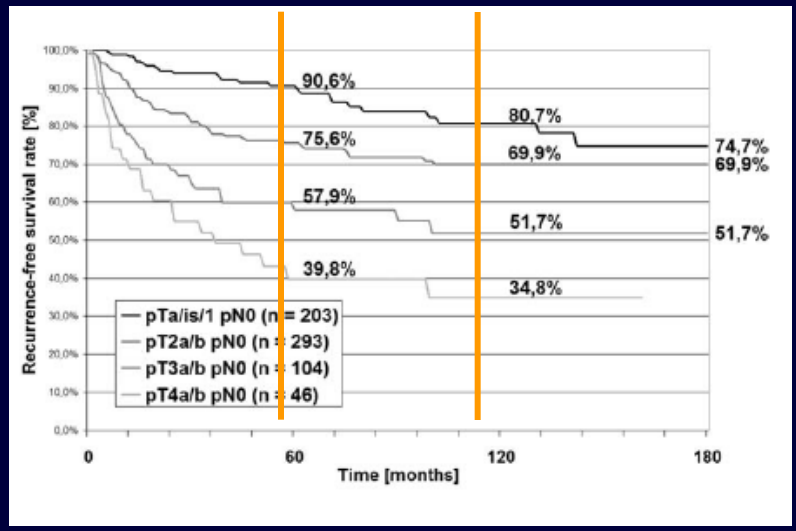

Hautmann et al. J Urol. 2005

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 (≤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.

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

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

= 20,2%

= 19,7%

Stein et al, J Clin Oncol 2001;19: 666-675

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.	%
Pathologic staging						
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

High-risk tumours	Any of the following: • T1 tumour • G3 (high grade) tumour • CIS • Multiple and recurrent and large (> 3 cm) Ta G1G2 tumours (all conditions must be presented in this point)

High Risk :

- ✓ **1st 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 1st 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

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