ΑΝΤΙΜΕΤΩΠΙΣΗ ΠΑΡΑΚΟΛΟΥΘΗΣΗ ΟΓΚΩΝ ΚΥΣΤΕΩΣ ΧΑΜΗΛΟΥ ΚΙΝΔΥΝΟΥ

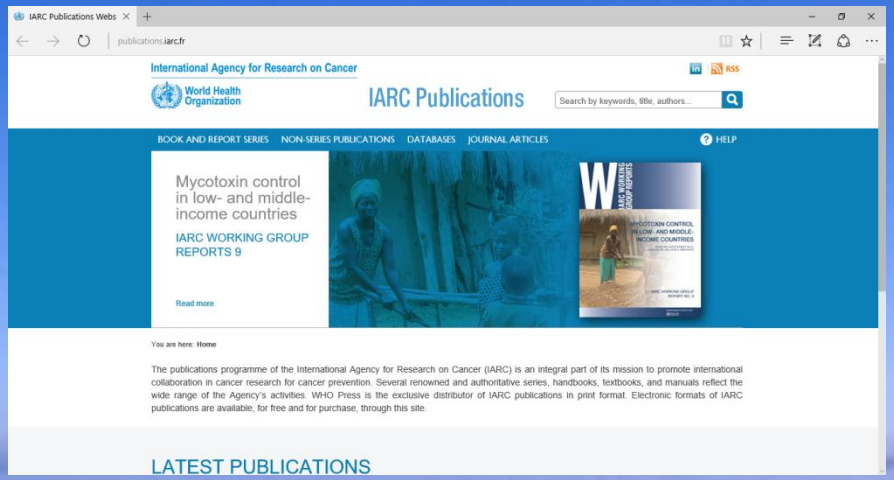
Κοριτσιάδης Γιώργος
Νοσοκομείο Μεταξά

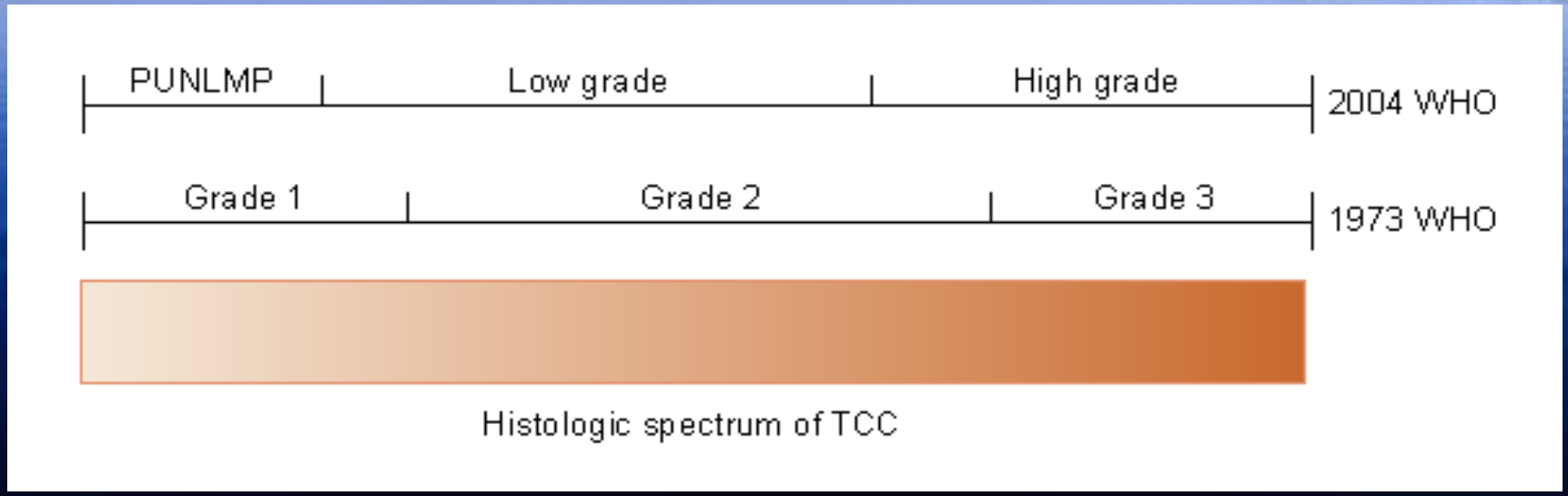
Κατηγοριοποίηση βάση της επικινδυνότητα του νεοπλάσματος για υποτροπή και πρόοδο της νόσου

Risk group stratification	Characteristics
Low-risk tumours	Primary, solitary, Ta, G1 (LG), < 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 (HG) tumour • CIS • Multiple and recurrent and large (> 3 cm) Ta G1G2 tumours (all conditions must be presented in this point)

Eur. Ass. U. Guide lines

ΣΤΑΔΙΟΠΟΙΗΣΗ





WHO ΚΑΤΗΓΟΡΙΟΠΟΙΗΣΗ 2016

Third edition [51]:	Fourth edition [1]:
Noninvasive urothelial lesions	*Noninvasive urothelial lesions*
Urothelial carcinoma in situ	Urothelial carcinoma in situ
Papillary urothelial carcinoma, low grade	Papillary urothelial carcinoma, low grade
Papillary urothelial carcinoma, high grade	Papillary urothelial carcinoma, high grade
Papillary urothelial neoplasm of low malignant potential	Papillary urothelial neoplasm of low malignant potential
Urothelial papilloma	Urothelial papilloma
Inverted urothelial papilloma	Inverted urothelial papilloma
	Urothelial proliferation of uncertain malignant potential (hyperplasia)
	Urothelial dysplasia

EUR UR 2016 IN PRESS

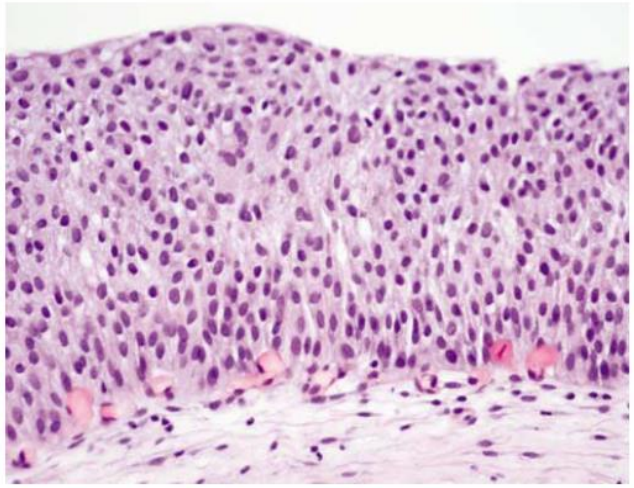


Figure 1 Urothelial hyperplasia. The urothelium is markedly thickened without significant architectural or cytologic abnormalities.

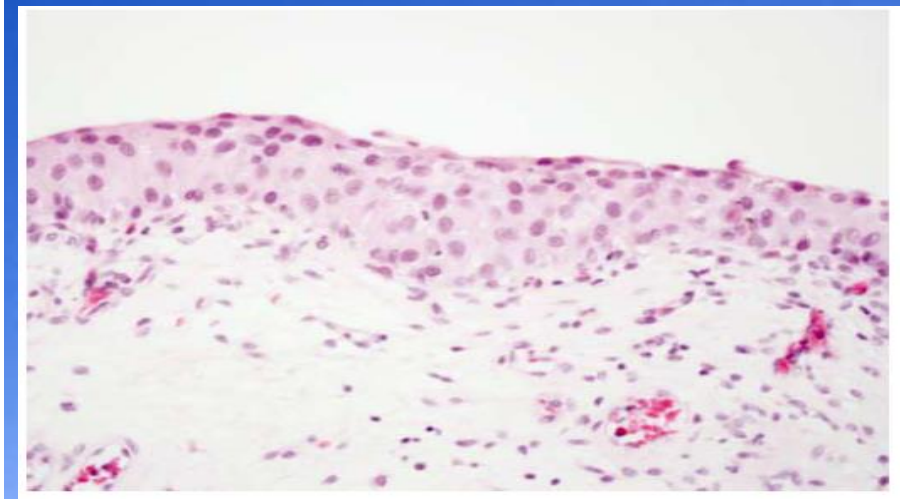


Figure 3 Urothelial dysplasia. There is mild nuclear enlargement with a somewhat haphazard distribution of nuclei within the urothelium. Note the mitotic figure in the upper level of the urothelium.

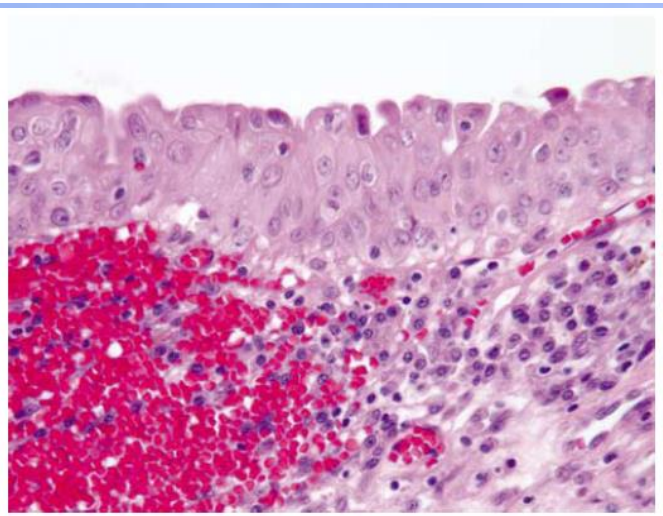


Figure 2 Reactive urothelial atypia. The nuclei are mildly enlarged, rounded and have small nucleoli. Note the intense chronic inflammatory infiltrate in the lamina propria.

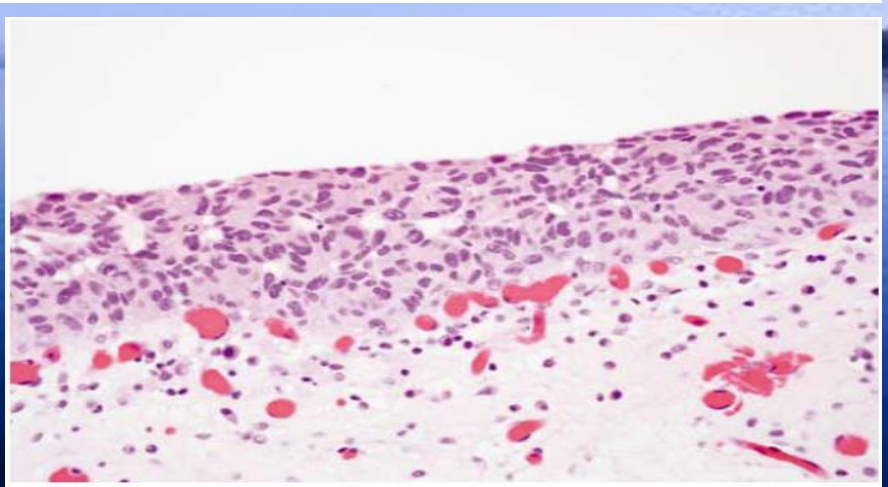


Figure 4 Urothelial carcinoma *in situ*. There is moderate nuclear enlargement and pleomorphism with a completely haphazard arrangement of the cells within the urothelium. A lesion similar to this may have been classified as moderate to severe dysplasia in the past but now it is included in the carcinoma *in situ* category.

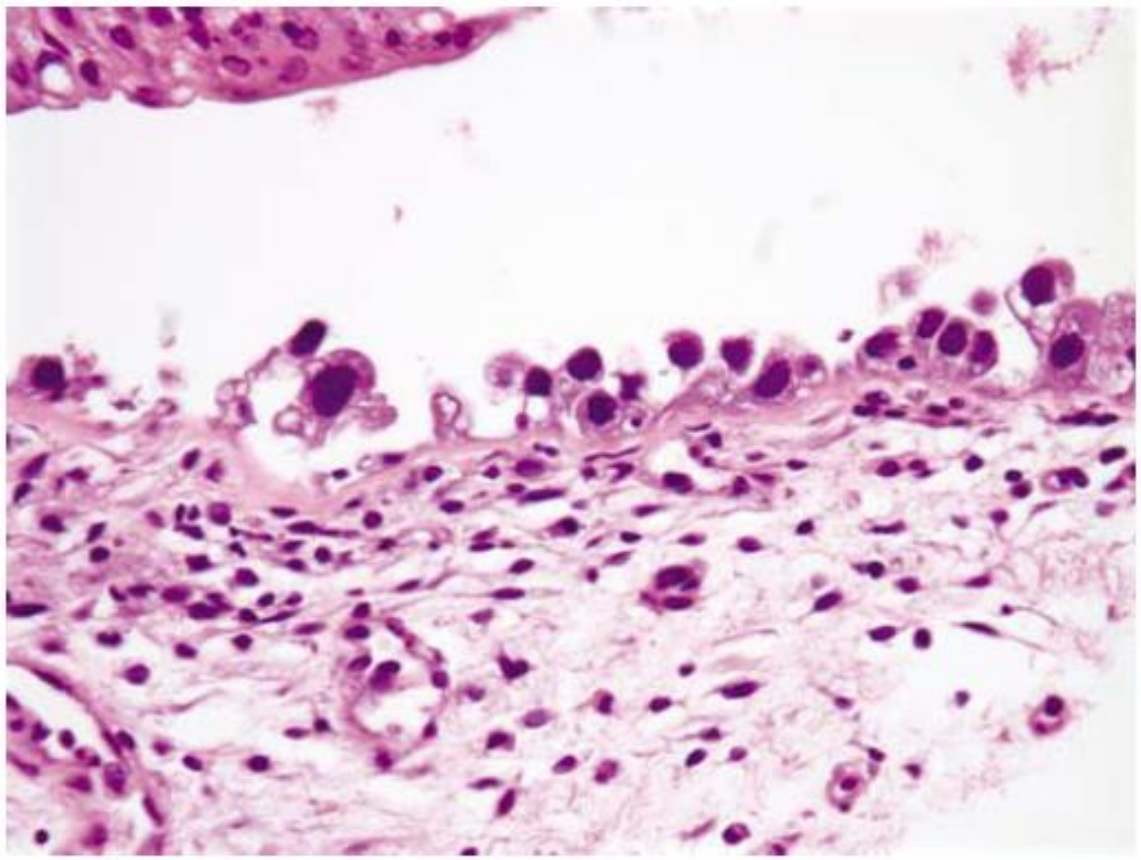
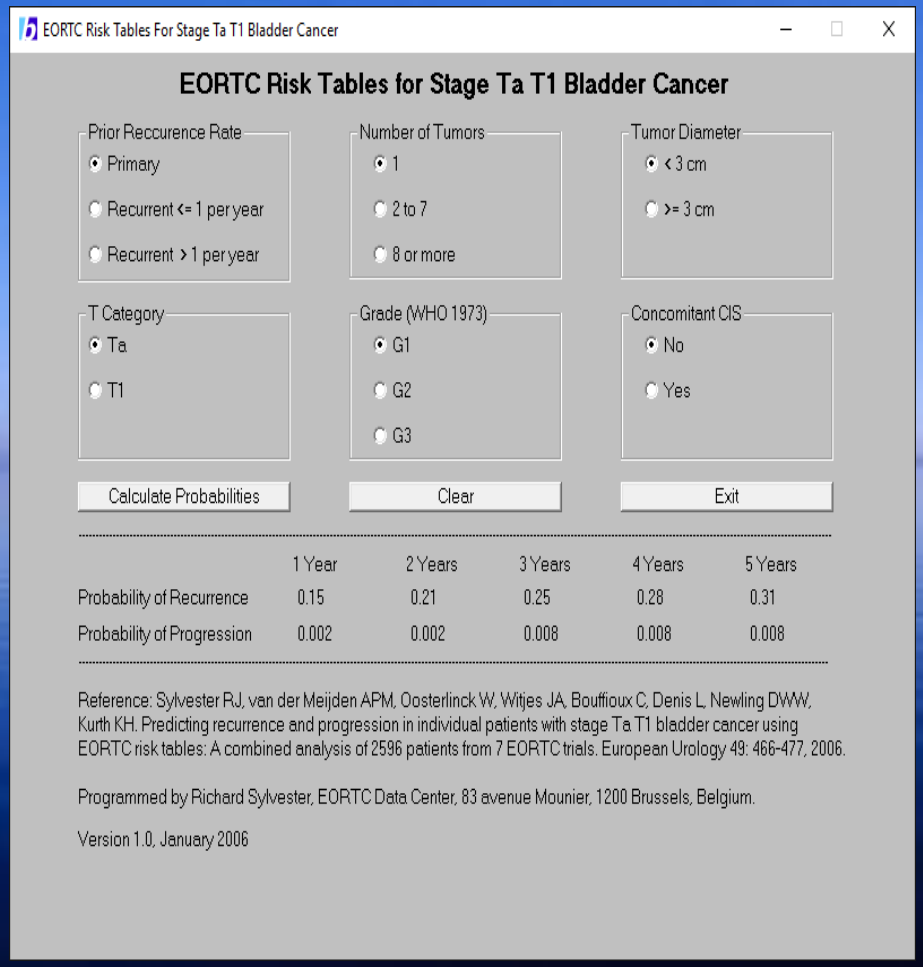


Figure 6 Urothelial carcinoma *in situ*. The denuding pattern is characterized by poorly cohesive cells that typically have large, pleomorphic and hyperchromatic nuclei.

EORTC & CUETO



El Modelo CUETO de Puntuacion — English

Factor		Puntuacion Recurrencia	Puntuacion Progresion
Sexo	Hombre	0	0
	Mujer	3	0
Edad (apos)	Menor que 60	0	0
	De 60 a 70	1	0
	Mayor que 70	2	2
Tumor recurrente	No	0	0
	Sv	4	2
NI tumores	Menor o igual a 3	0	0
	Mayor que 3	2	1
Categorva T	Ta	0	0
	T1	0	2
Tis asociado	No	0	0
	Sv	2	1
Grado	G1	0	0
	G2	1	2
	G3	3	6
Puntuaciones totales		0	0

Probabilidad de recurrencia y progresion a 1, 2 y 5 apos por puntuacion total				
Tiempo	Recurrencia (0-4)		Progresion (0-4)	
	Prob. (%)	I.C. 95% (L.Inf-L.Sup)	Prob. (%)	I.C. 95% (L.Inf-L.Sup)
1 apo	8.24	(5.91-10.57)	1.17	(0.15- 2.19)
2 apos	12.60	(9.76-15.44)	2.16	(0.77- 3.55)
5 apos	20.98	(17.33-24.63)	3.76	(1.90- 5.62)

Φυσική εξέλιξη των νεοπλασμάτων χαμηλού κινδύνου

5 ετία

TABLE 4. *Frequency of tumor recurrence and treatments by tumor type*

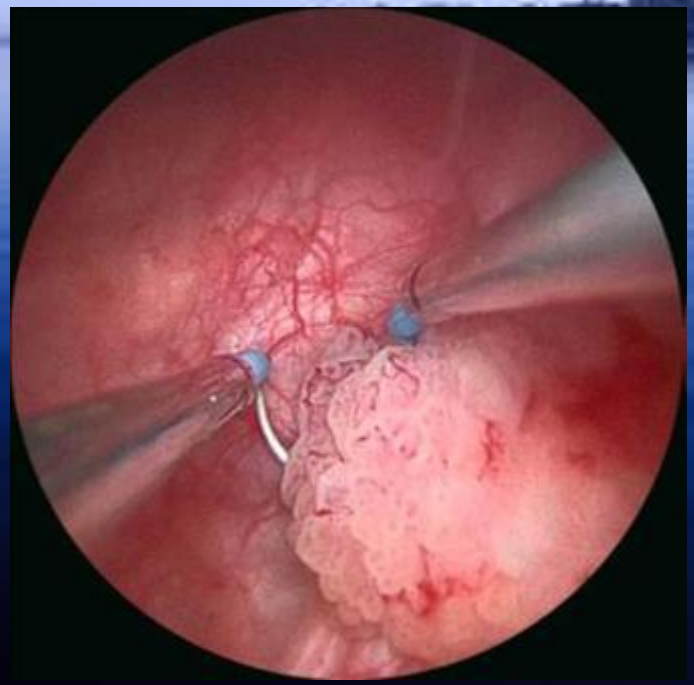
	Mean Recurrence (range)*	Mean Tumors/Yr (range)	Mean TURs (range)	Mean TURs/Yr (range)	Mean Fulgurations (range)	Mean Fulgurations/Yr (range)
Papilloma	1.2 (0–12)	0.12 (0–1.2)	0.2 (0–2)	0.02	1.0 (0–10)	0.11
PUNLMP	1.7 (0–10)	0.20 (0–1.0)	0.37 (0–2)	0.06	1.3 (1–8)	0.19
TaLG	4.7 (0–19)	0.62 (0–3.4)	1.6 (0–8)	0.27	3.1 (0–16)	0.47
p Value	0.01	0.001	0.003	0.01	0.01	0.02
Totals						
All pts	4.1	0.53 (0–3.4)	1.4 (0–8)	0.22 (0–3)	2.7 (0–16)	0.41 (0–2.2)
Pts with recurrence	6.2 (1–19)	0.79 (0.1–3.4)	2.1 (0–8)	0.34 (0–3)	4.1 (0–16)	0.61 (0–2.2)

* Mean number of positive cystoscopies for tumor recurrence.

J.U 178 pg 1201

Φυσική εξέλιξη των νεοπλασμάτων χαμηλού κινδύνου

τουλάχιστον μία διουρηθρική κάθε 3 χρόνια



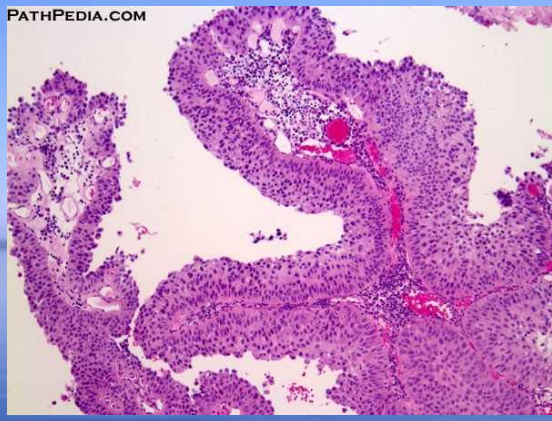
Φυσική εξέλιξη των νεοπλασμάτων χαμηλού κινδύνου

Είναι σπάνια η πρόοδος της νόσου για τα νεοπλάσματα χαμήλου κινδύνου υποτροπής

Μόνο 8% για τα pTaG1 στην 5ετία

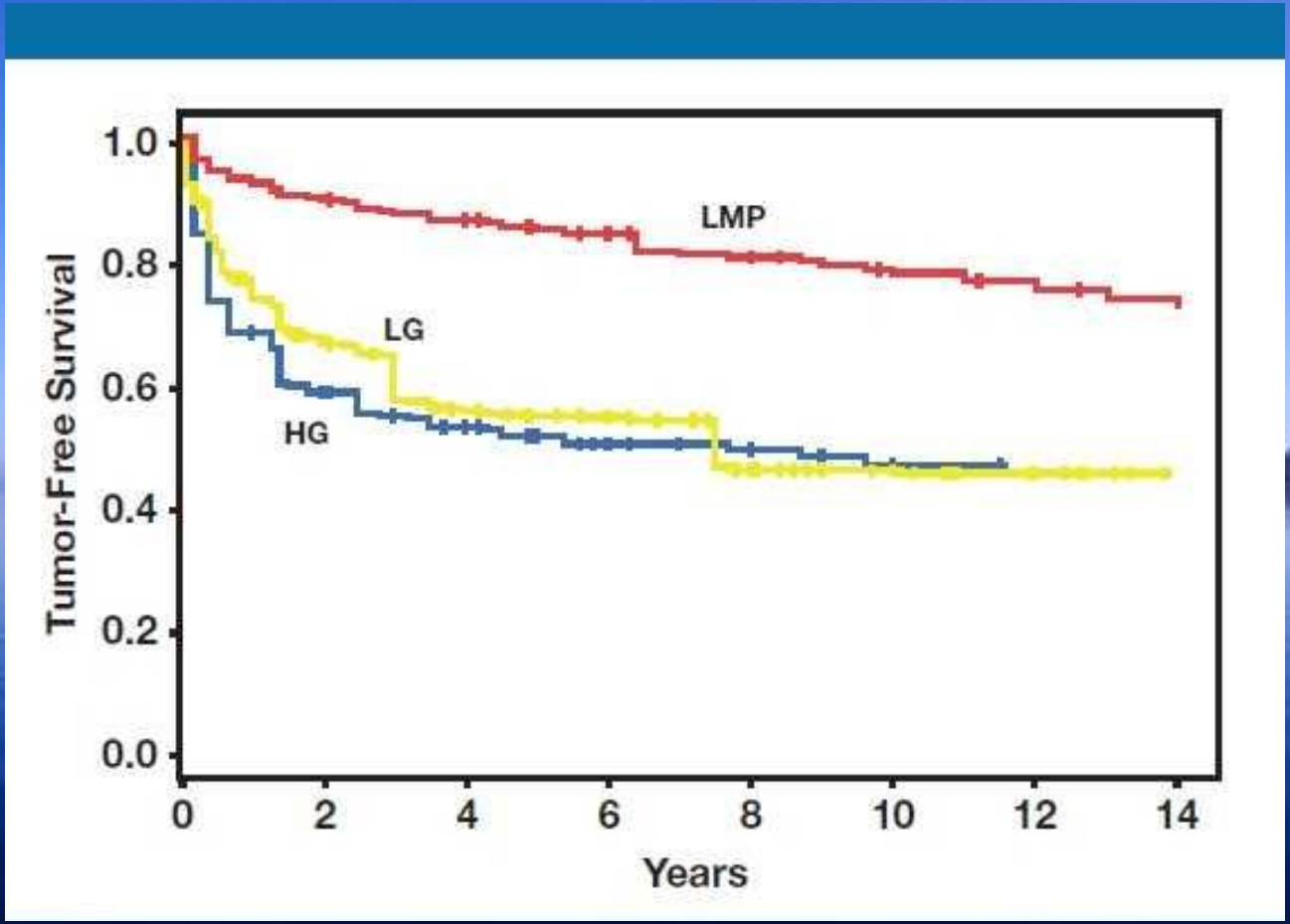
Σχεδόν μηδενική για τα PUNLMP

<8% θα αναπτύξει TCC στην ανώτερη αποχετευτική μοίρα από τα pTa



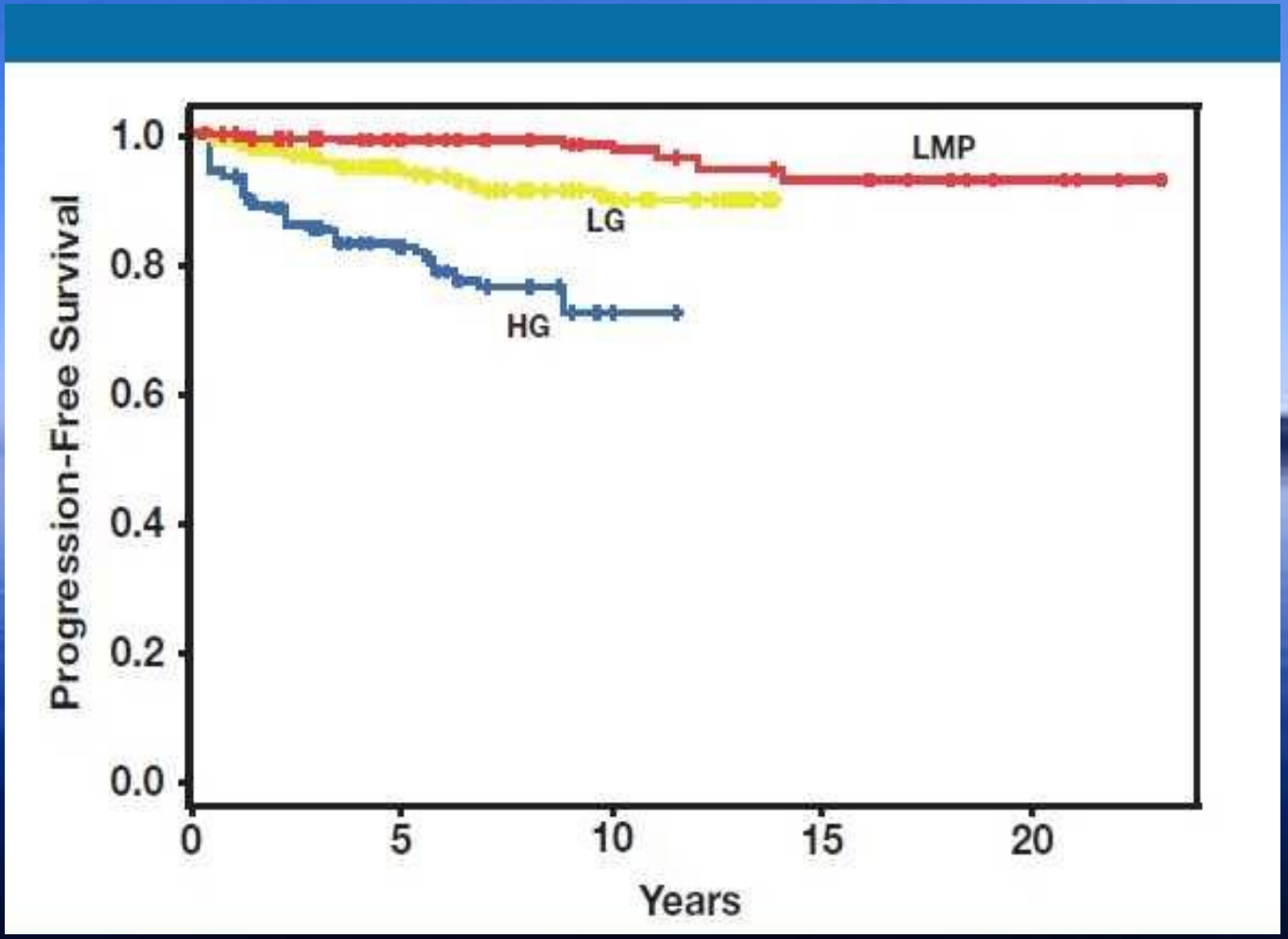
J.U 178 pg 1201

A Kaplan-Meier plot of the probability of being tumor free vs years of follow-up for all patients, regardless of their tumor grade. For this analysis, there were 4,050 patients.



AM J of SOCIETY OF CLINICAL PATHOLOGY

A Kaplan-Meier plot of the probability of being tumor free vs years of follow-up for all patients, regardless of their tumor grade. For this analysis, there were 4,050 patients.



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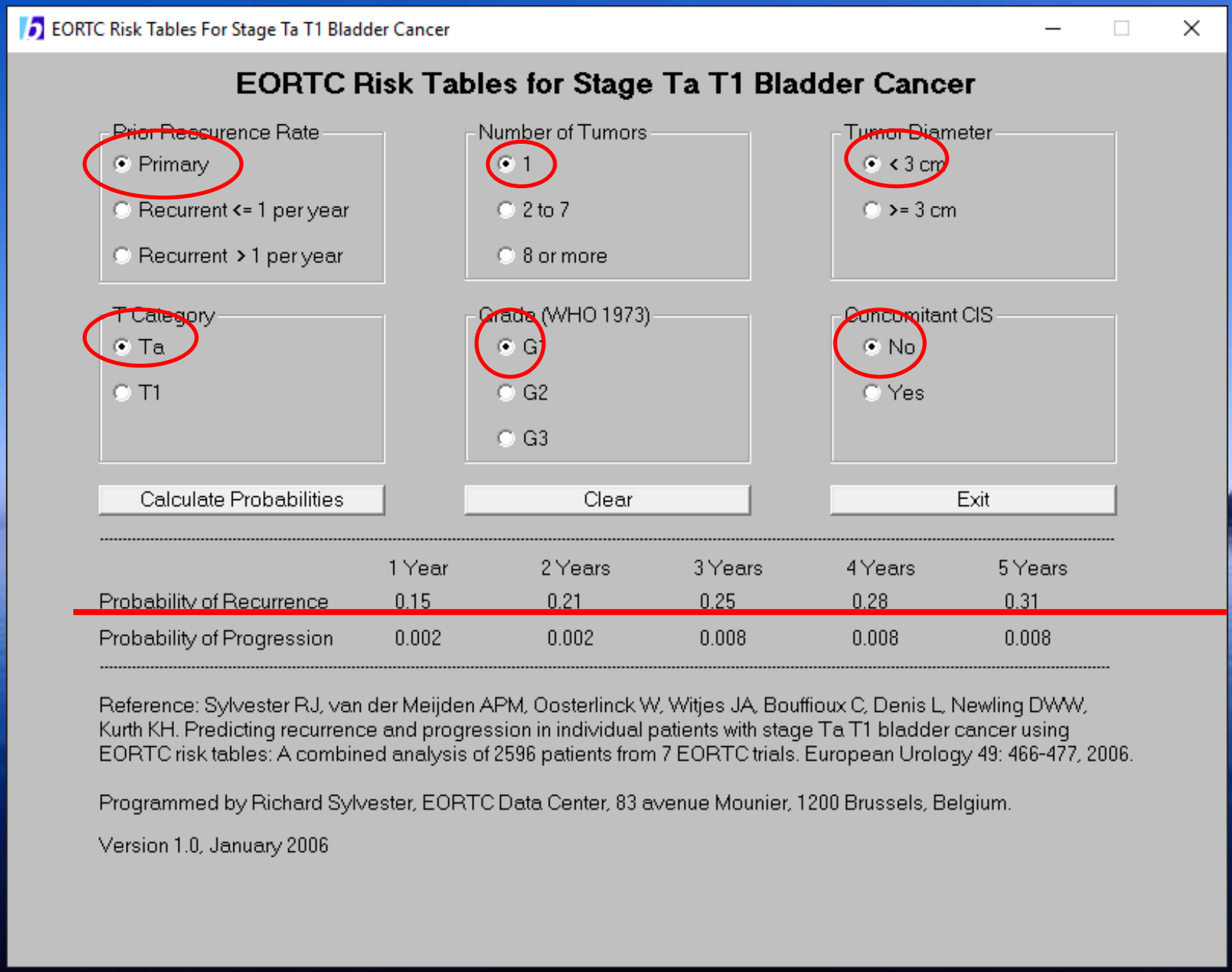
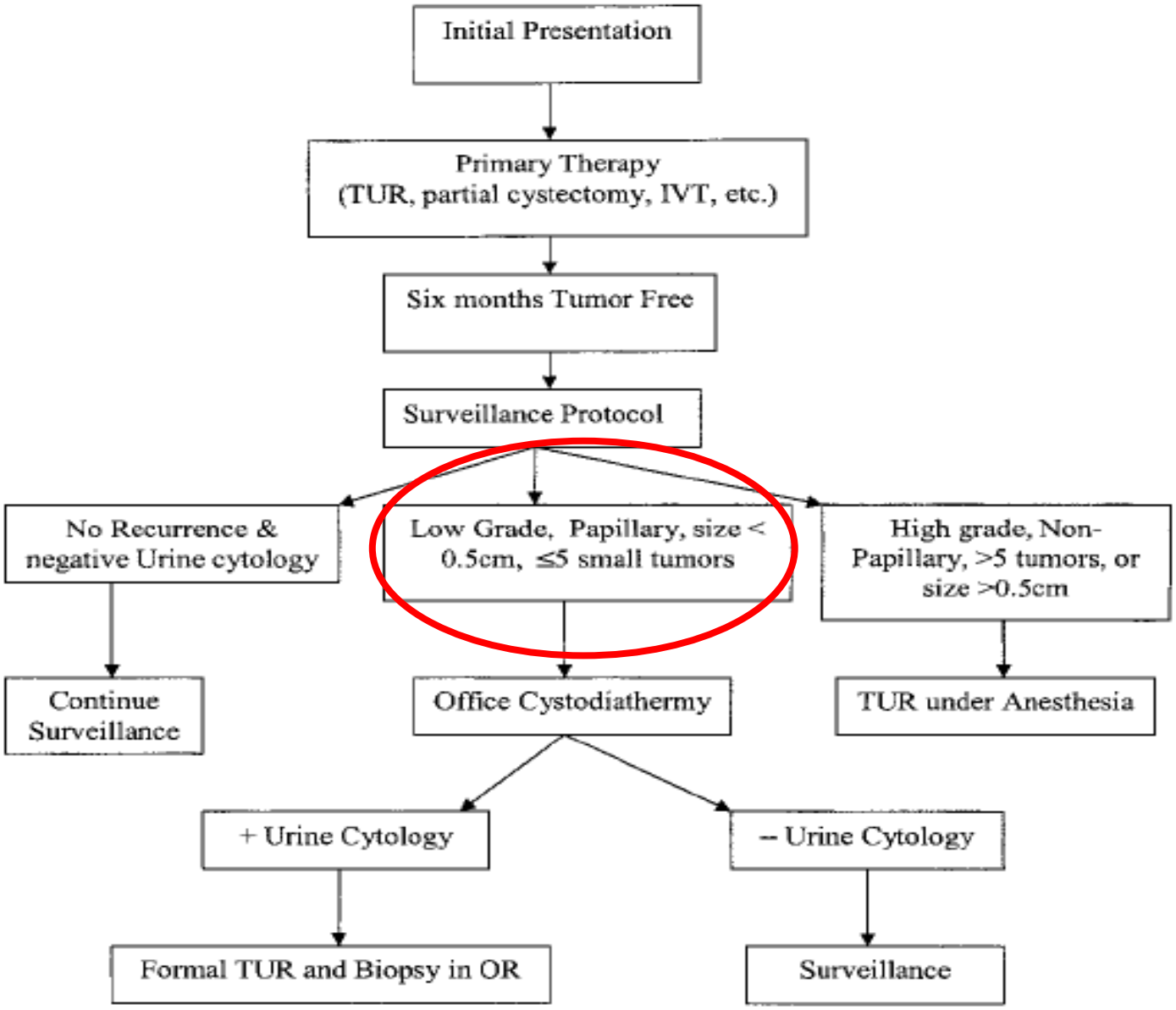
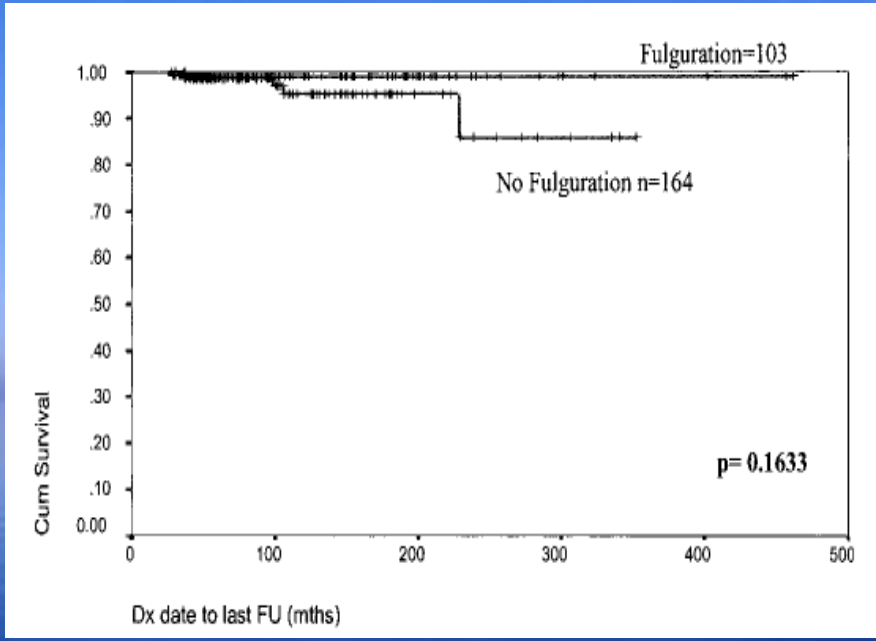

EORTC Risk Tables For Stage Ta T1 Bladder Cancer
EORTC Risk Tables for Stage Ta T1 Bladder Cancer
Prior Recurrence Rate
Primary
Recurrent <= 1 per year
Recurrent > 1 per year
Number of Tumors
1
2 to 7
8 or more
Tumor Diameter
< 3 cm
>= 3 cm
T Category
Ta
T1
Grade (WHO 1973)
G1
G2
G3
Concomitant CIS
No
Yes
Calculate Probabilities
Clear
Exit
1 Year
2 Years
3 Years
4 Years
5 Years
Probability of Recurrence
0.15
0.21
0.25
0.28
0.31
Probability of Progression
0.002
0.002
0.008
0.008
0.008
Reference: Sylvester RJ, van der Meijden APM, Oosterlinck W, Witjes JA, Bouffioux C, Denis L, Newling DWW, Kurth KH. Predicting recurrence and progression in individual patients with stage Ta T1 bladder cancer using EORTC risk tables: A combined analysis of 2596 patients from 7 EORTC trials. European Urology 49: 466-477, 2006.
Programmed by Richard Sylvester, EORTC Data Center, 83 avenue Mounier, 1200 Brussels, Belgium.
Version 1.0, January 2006

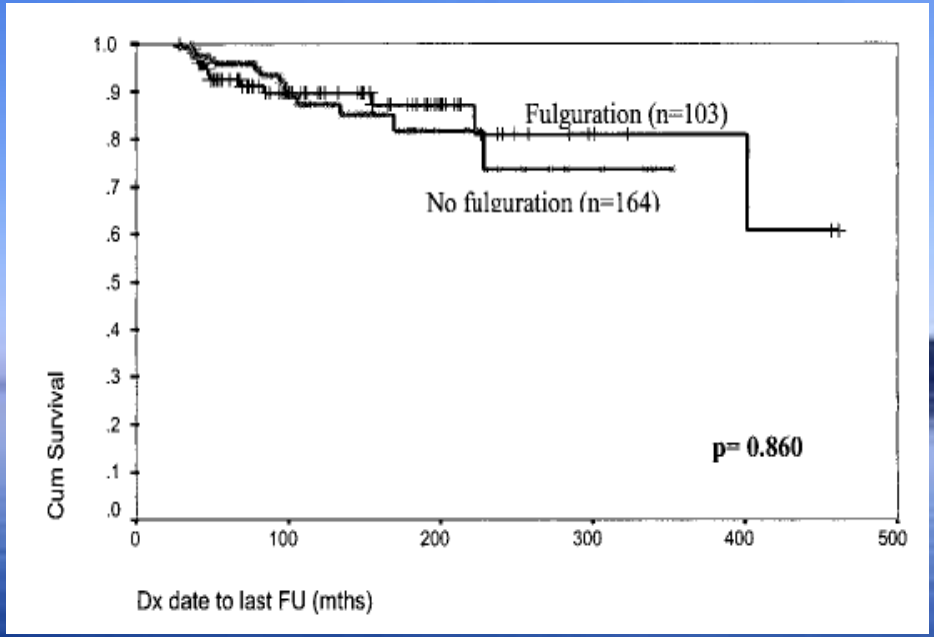
Office fulguration



Donat et all. J Ur 171 pg636

OFFICE FULGARATION





DSS

the period after curative when no disease

PROGRESION

Μπορούμε να στηριχτούμε στην κυστεοσκόπηση για το τελικό αποτέλεσμα της ιστολογικής ?

Τα μονήρη μικρών διαστάσων low Grade νεοπλάσματο μπορούν να αναγνωριστούν με ακρίβεια 93%

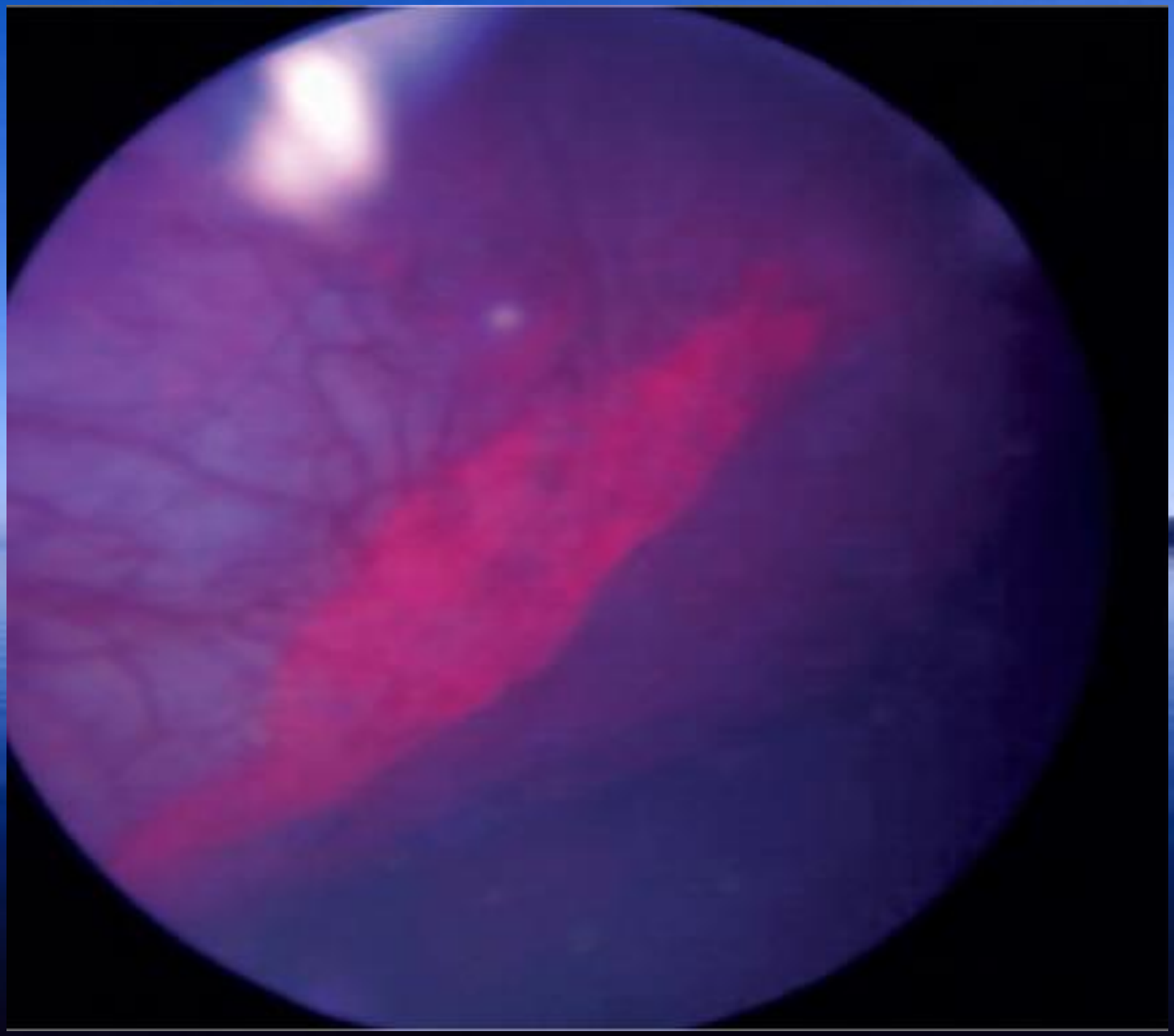
αν προστεθεί και η κυττ. Ούρων τοτε σχεδόν σίγουρα μπορείς να προδικάσεις την τελική ιστολογική

J Urol, **168:** 978, 2002

Η κυστεοσκόπηση έχει ευαισθησία και ειδικότητα

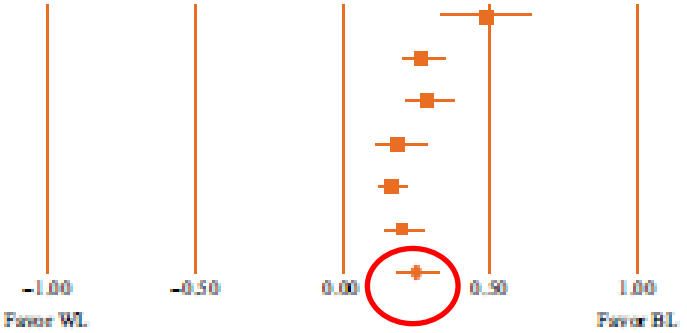
- Μπορεί να χάσει ενα 22.6% νεοπλασμάτων **pTa** και **T1**
- και 25% των in CIS

Bruger et.al. Eu.U 2013. 64



Αναγνωρίζει περισσότερα pTa-pT1

Study	Patients with Additional Tumours (%)	*p*	Relative Weight
Jichlinski et al [22]	20/ 41 (48.8)	<0.001	13.90
Schmidbauer et al [12]	41/154 (26.6)	<0.001	18.04
Grossman et al [19]	35/121 (28.9)	<0.001	17.48
Jocham et al [8]	14/ 75 (18.7)	<0.001	14.40
Stenzl et al [21]	47/286 (16.4)	<0.001	18.71
Burgués et al [23]	31/154 (20.1)	<0.001	17.48
Overall	188/831 (24.9*)	<0.001	



Cochran *Q* test for Heterogeneity 25.636 ($p = 0.000$)
I^2 80.496

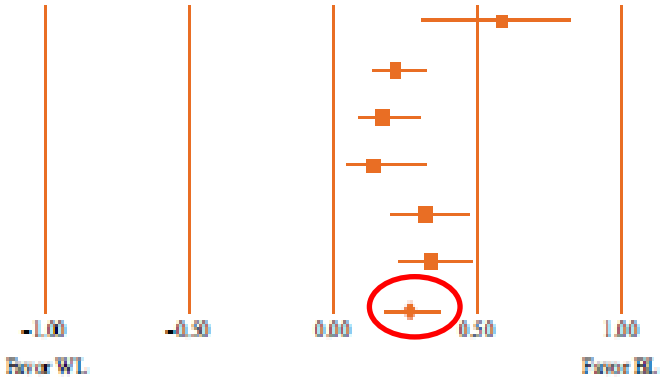
*Weighted overall results from the random-effects meta analysis.

The population used for this analysis consists of those patients with at least one Ta or T1 lesion.

Fig. 2 – Meta-analysis: patients with at least one Ta or T1 lesion seen only with blue light (BL). CI = confidence interval; WL = white light.

CIS

Study	Patients with Additional Tumours (%)	*p*	Relative Weight
Jichlinski et al [22]	7/ 12 (58.3)	<0.001	10.89
Schmidbauer et al [12]	17/ 80 (21.3)	<0.001	20.92
Grossman et al [19]	9/ 53 (17.0)	<0.001	17.39
Jocham et al [8]	4/ 29 (13.8)	<0.001	12.02
Stenzl et al [21]	13/ 41 (31.7)	<0.001	18.51
Burgués et al [23]	18/ 53 (34.0)	<0.001	20.27
Overall	68/268 (26.7*)	<0.001	



Cochran *Q* test for Heterogeneity 13.231 ($p = 0.021$)

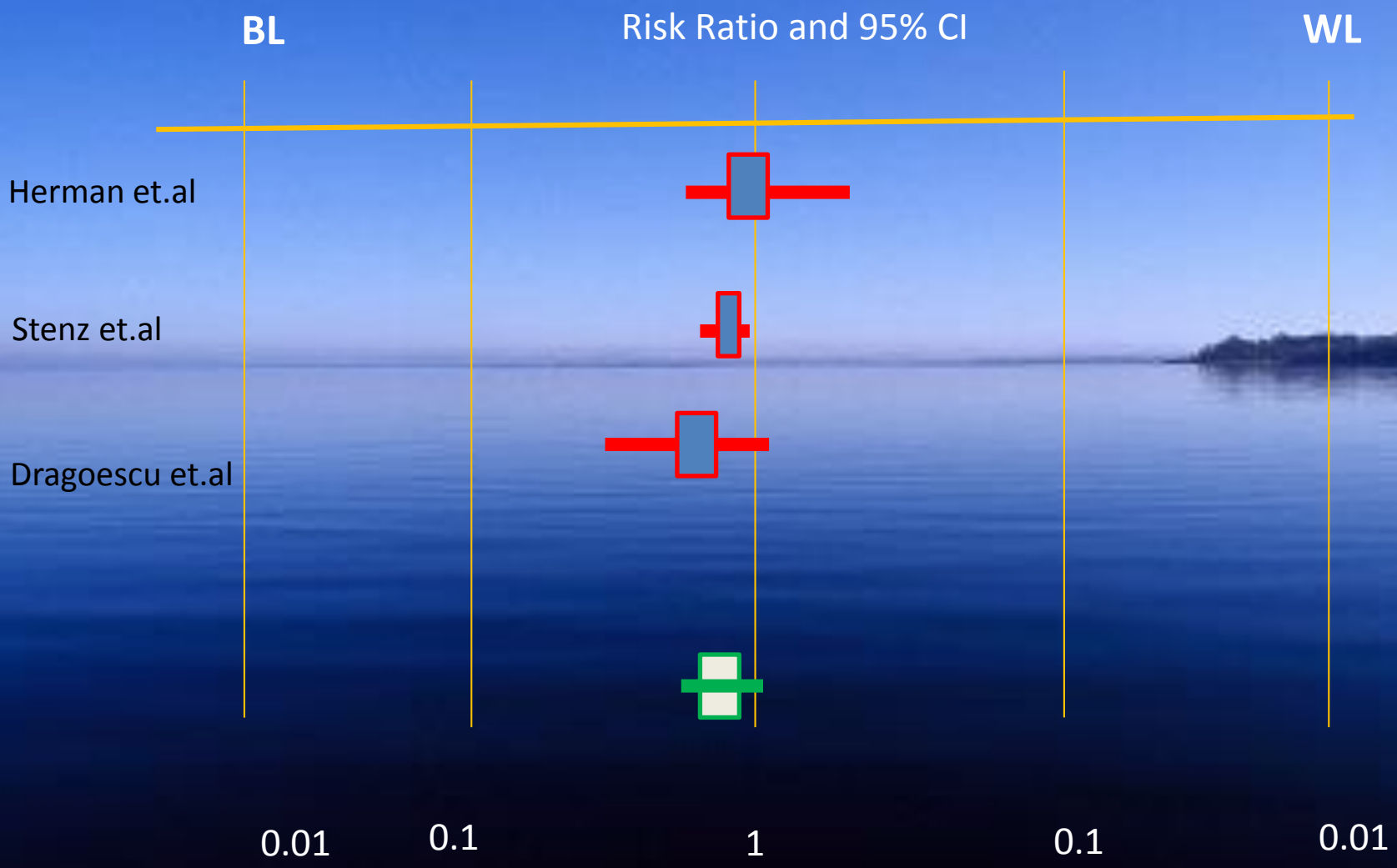
I^2 62.209

*Weighted overall results from the random-effects meta-analysis.

The population used for this analysis consists of those patients with at least one CIS lesion.

Fig. 3 – Meta-analysis: patients with at least one carcinoma in situ (CIS) lesion seen only with blue light (BL) where no CIS lesions were seen with white light (WL). CI = confidence interval.

Meta-analysis Υποτροπή στους 12 μήνες



Υποτροπή

Table 6 – Overall recurrence rates up to 12 months

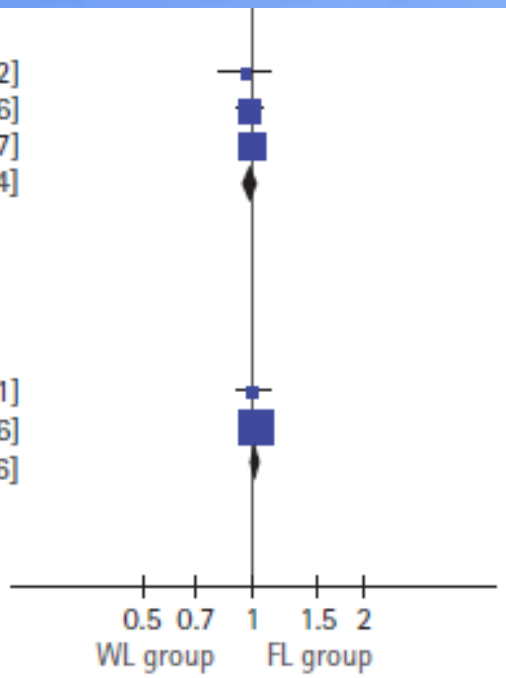
	Patients treated with BL, n (%)	Patients treated with WL, n (%)	Total	Follow-up period
Hermann et al. [24]	27/68 (39.7)	38/77 (49.4)	145	12 mo
Stenzl et al. [21]	72/200 (36.0)	92/202 (45.5)	402	9 mo
Drăgoescu et al. [25]	8/42 (19.0)	17/45 (37.8)	87	12 mo
Total	107/310 (34.5)	147/324 (45.4)	634*	p = 0.006; RR = 0.761 (0.627–0.924)
At least one T1 or CIS	26/74 (35.1)	45/87 (51.7)	161*	p = 0.052; RR = 0.696 (0.482–1.003)
At least one Ta	92/256 (35.9)	119/268 (44.4)	524*	p = 0.040; RR = 0.804 (0.653–0.991)
High-risk subgroup	46/126 (36.5)	70/144 (48.6)		p = 0.05; RR = 0.752 (0.565–1.000)
Intermediate-risk subgroup	43/95 (45.3)	40/74 (54.1)		p = 0.246; RR = 0.836 (0.617–1.132)
Low-risk subgroup	14/78 (17.9)	34/98 (34.7)		p = 0.029; RR = 0.561 (0.334–0.944)

BL = blue light; CIS = carcinoma in situ; RR = risk ratio; WL = white light.

Some patients appear in both subgroups (at least one T1 or CIS and at least one Ta).

ΠΡΟΟΔΟΣ ΤΗΣ ΝΟΣΟΥ
OS and CSS

5.1.3 PFS at 12 months						
Drăgoescu 2011 et al.	20	22	21	22	9.7%	0.95 [0.81, 1.12]
Schumacher 2010 et al.	123	138	128	141	40.8%	0.98 [0.91, 1.06]
Stenzl 2011 et al.	157	176	164	183	49.5%	1.00 [0.93, 1.07]
Subtotal (95% CI)		336		346	100.0%	0.99 [0.94, 1.04]
Total events	300		313			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.26$, df = 2 (P = 0.88); $I^2 = 0\%$						
Test for overall effect: Z = 0.57 (P = 0.57)						
5.1.4 PFS at 24 months						
Babjuk 2005 et al.	55	60	57	62	11.6%	1.00 [0.90, 1.11]
Burger 2009 et al.	138	142	261	274	88.4%	1.02 [0.98, 1.06]
Subtotal (95% CI)		202		336	100.0%	1.02 [0.98, 1.06]
Total events	193		318			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.18$, df = 1 (P = 0.67); $I^2 = 0\%$						
Test for overall effect: Z = 0.94 (P = 0.35)						



2012 BJU INTERNATIONAL | 110, E209–E215

BLUE LIGHT ΠΟΤΕ ?

ΣΤΗΝ ΠΡΩΤΗ TUR-BT

ΠΟΛΥΕΣΤΙΑΚΟ

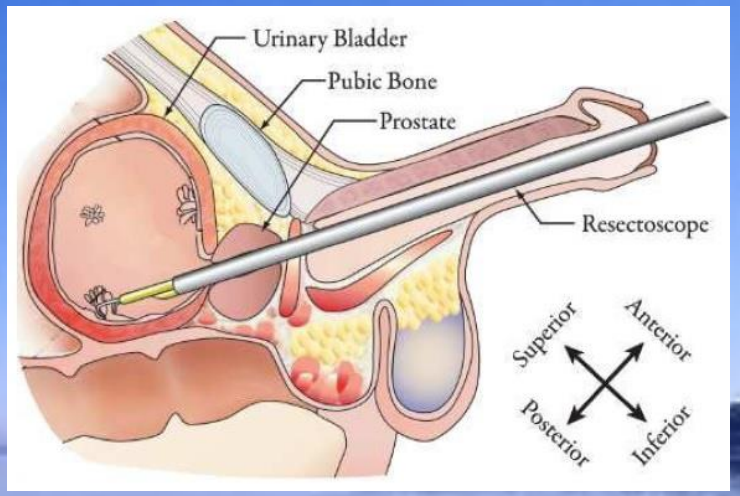
ΣΤΑ IN CITU

BURGER ET.AL EUR UR (64) 2013

Gold standard Tur-BT

Tur bt

Ογκολογική επέμβαση

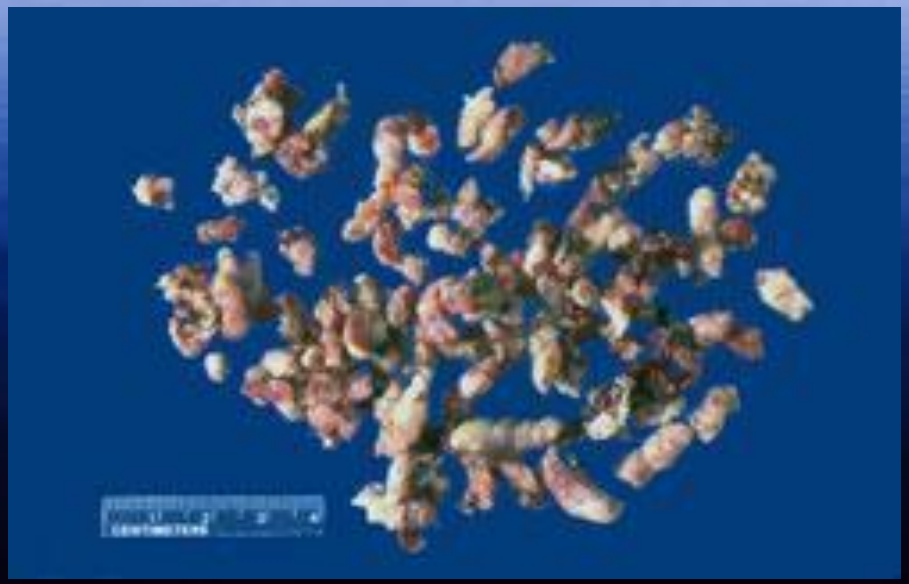


- Ριζικός στην αντιμετώπιση
- Θεραπευτικός
- Χωρίς επιπλοκές

Tur BT

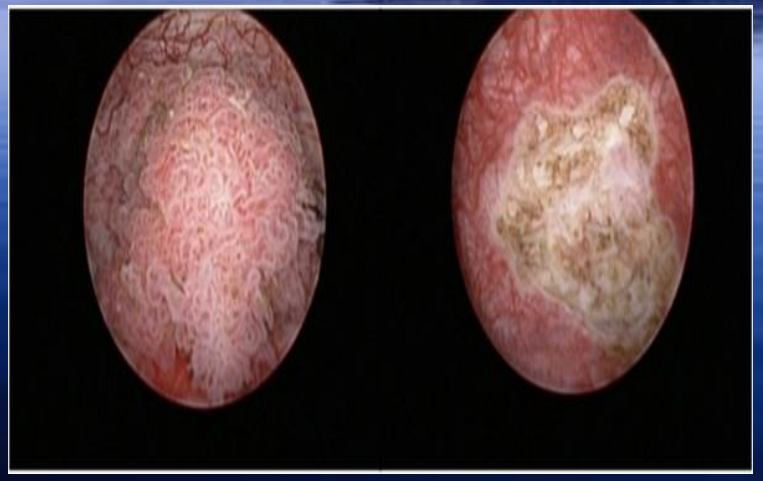
Η μοναδική ογκολογική επέμβαση

που το νεόπλασμα αφαιρείται σε πολλαπλά τεμάχια και όχι en block



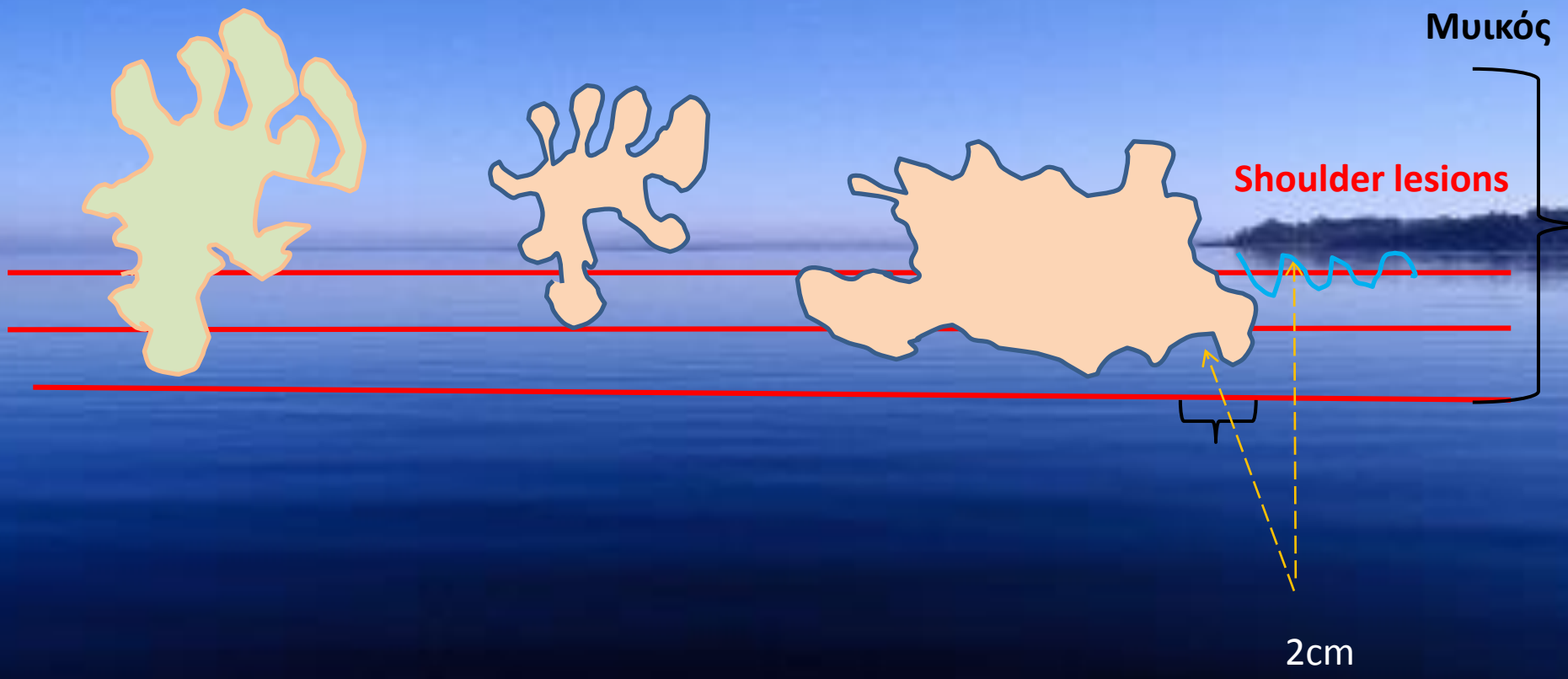
Βασικές αρχές

- >1 cm μπορεί να αφερεθεί en block
- Η διουρηθρική μας επεκτείνεται 2cm στην περιφέρεια
- Νεόπλασμα από διαφορετικές θέσεις στέλνονται διαφορετικά
- Αν δεν έχουμε μυικό επιστρέφουμε σε 6 w (βασική προυπόθεση να μην υπάρχει υπολοιπόμενος όγκος)
- Σε μεγαλύτερα νεοπλάσματα η βάση πρέπει να στέλνεται ξεχωριστά



Guide lines

Tur BT

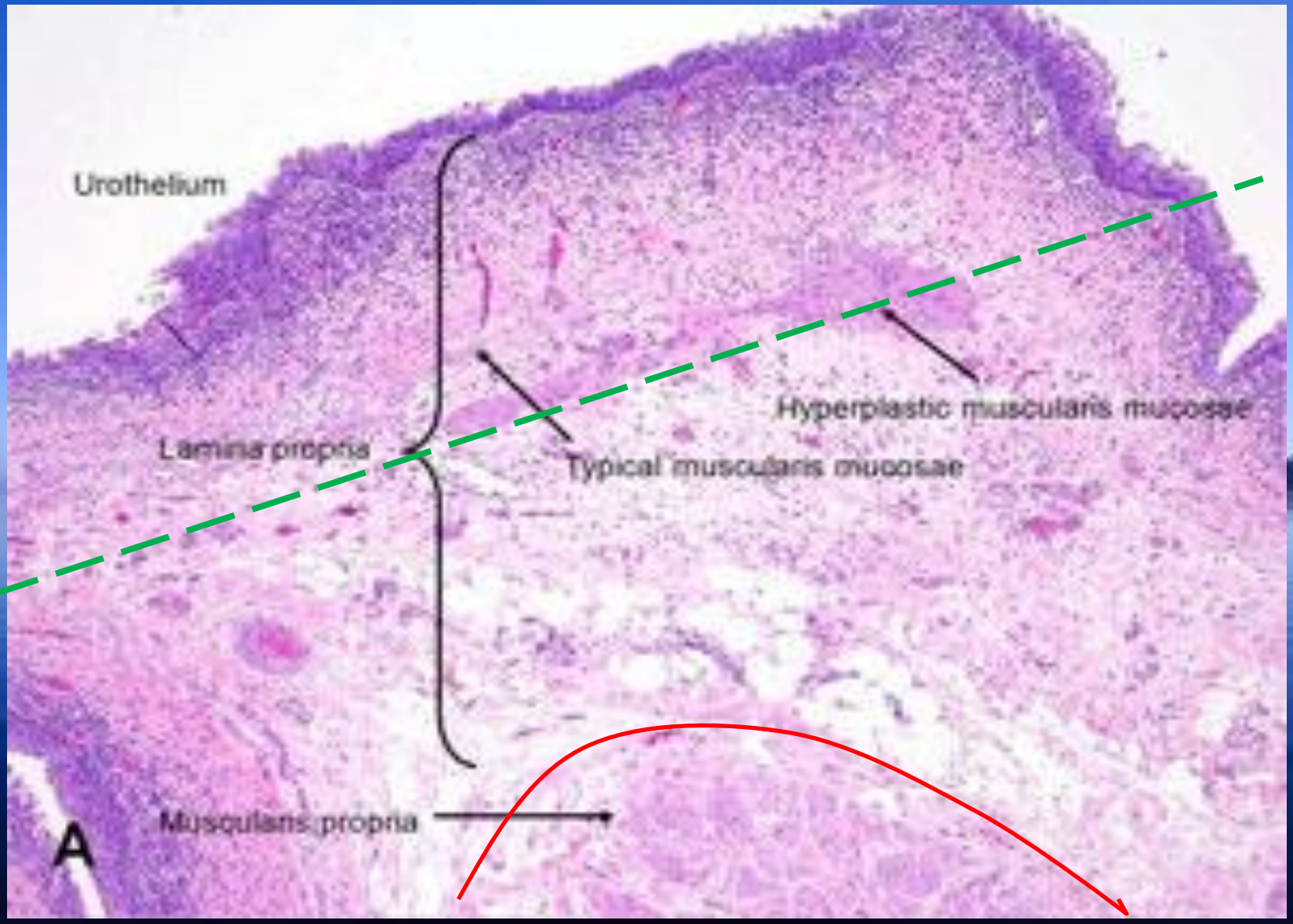


Modern Pathology (2009) 22

pTa

«Interobserver variability in diagnosing lamina propria invasion is substantial, 35% of carcinomas initially diagnosed as stage pT1 were downstaged to pTa, and 3% were upstaged as pT2-4 carcinomas»

Modern Pathology (2009) 22, S70–S95



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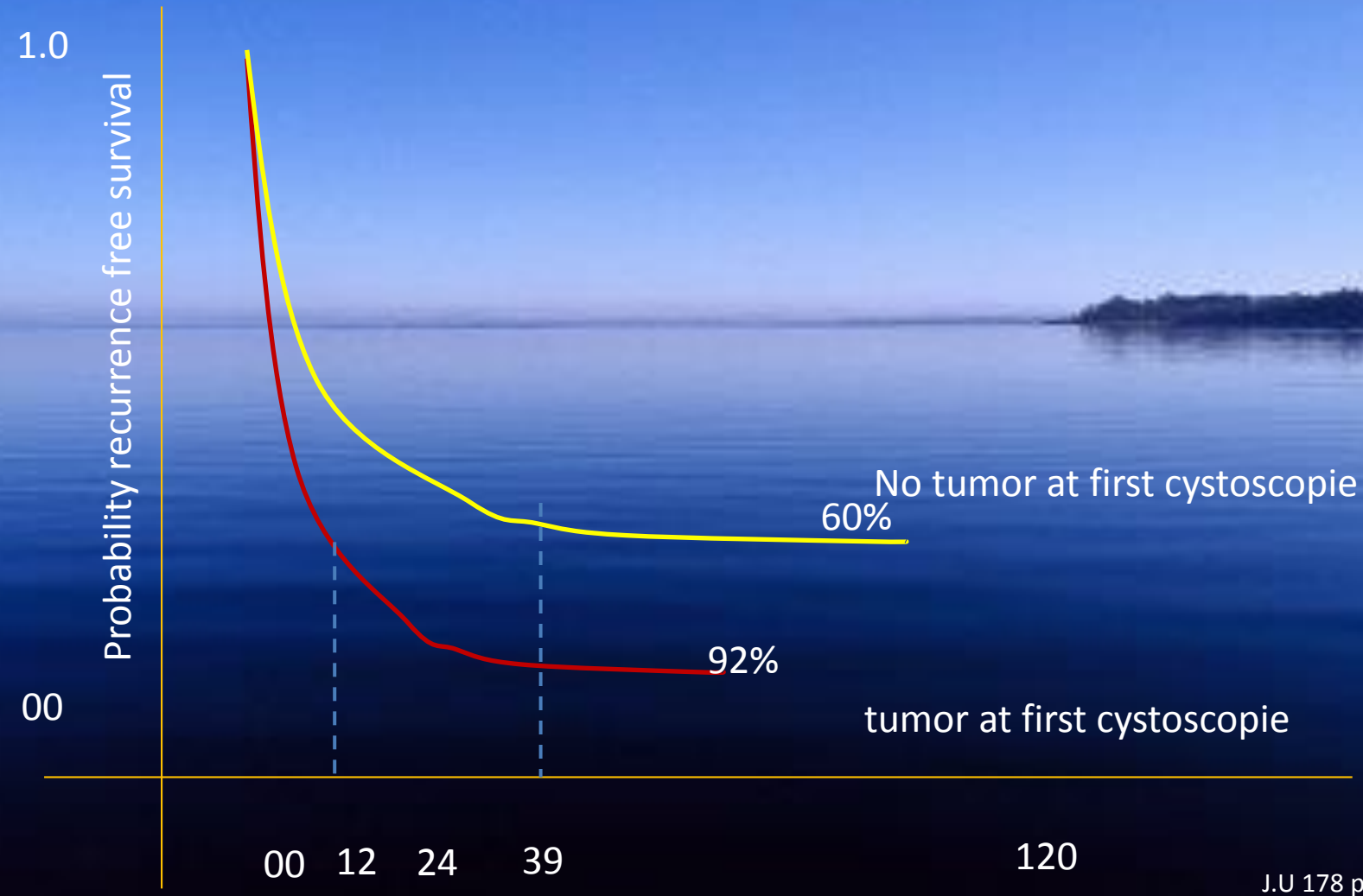
Σημασία της κυστεοσκόπησης στους τρείς μήνες για τις υποτροπές στα pTa



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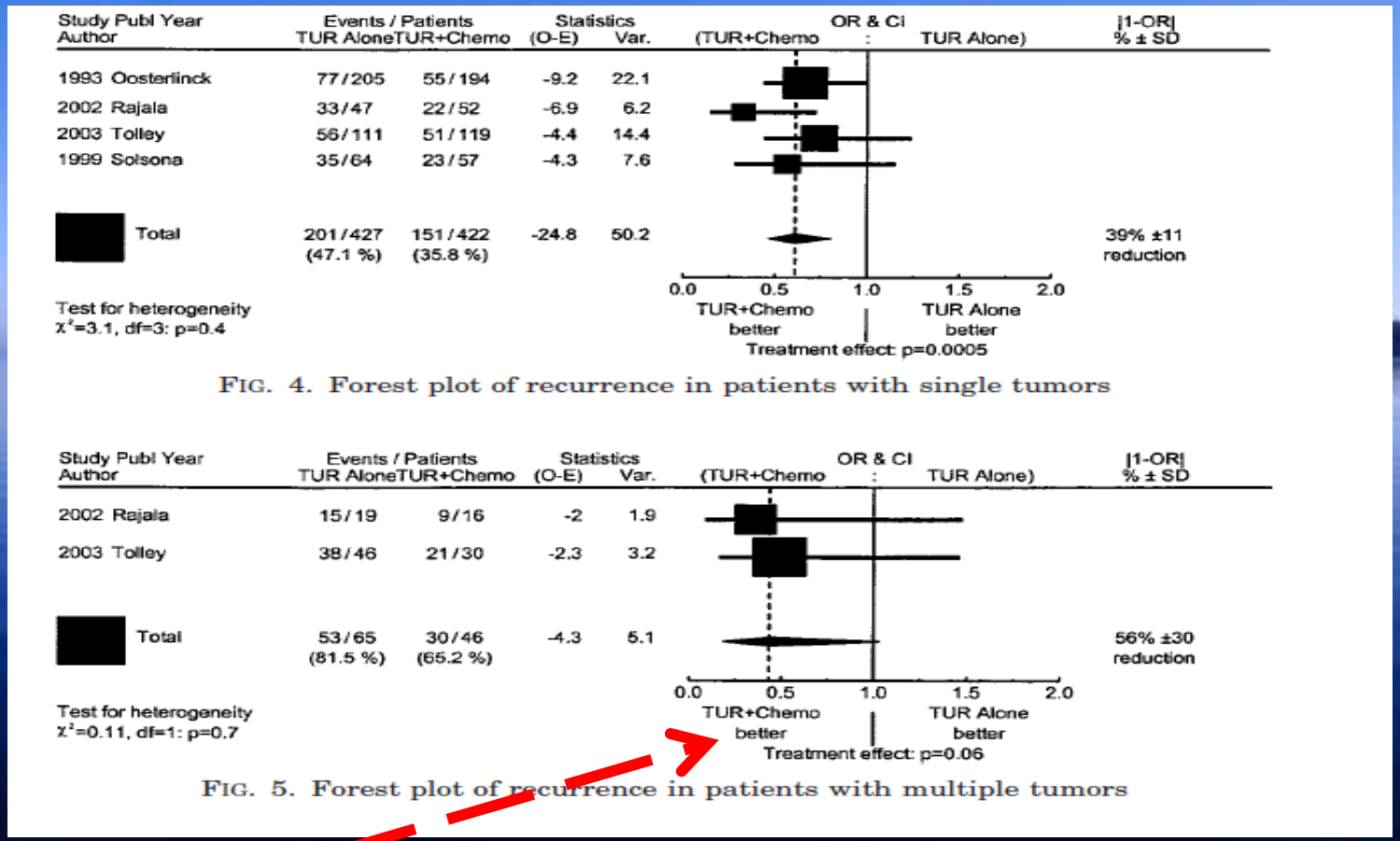

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Platinum Priority – Guidelines

Editorial by J. Alfred Witjes on pp. 245–246 of this issue

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?

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Abstract

Context: The European Association of Urology non–muscle-invasive bladder cancer (NMIBC) guidelines recommend that all low- and intermediate-risk patients receive a single immediate instillation of chemotherapy after transurethral resection of the bladder (TURB), but its use remains controversial.
Objective: To identify which NMIBC patients benefit from a single immediate instillation.
Evidence acquisition: A systematic review and individual patient data (IPD) meta-analysis of randomized trials comparing the efficacy of a single instillation after TURB with TURB alone in NMIBC patients was carried out.
Evidence synthesis: A total of 13 eligible studies were identified. IPD were obtained for 11 studies randomizing 2278 eligible patients, 1161 to TURB and 1117 to a single instillation of epirubicin, mitomycin C, pirarubicin, or thiotepa. A total of 1128 recurrences, 108 progressions, and 460 deaths (59 due to bladder cancer [BCa]) occurred. A single instillation reduced the risk of recurrence by 35% (hazard ratio [HR]: 0.65; 95% confidence interval [CI], 0.58–0.74; $p < 0.001$) and the 5-yr recurrence rate from 58.8% to 44.8%. The instillation did not reduce recurrences in patients with a prior recurrence rate

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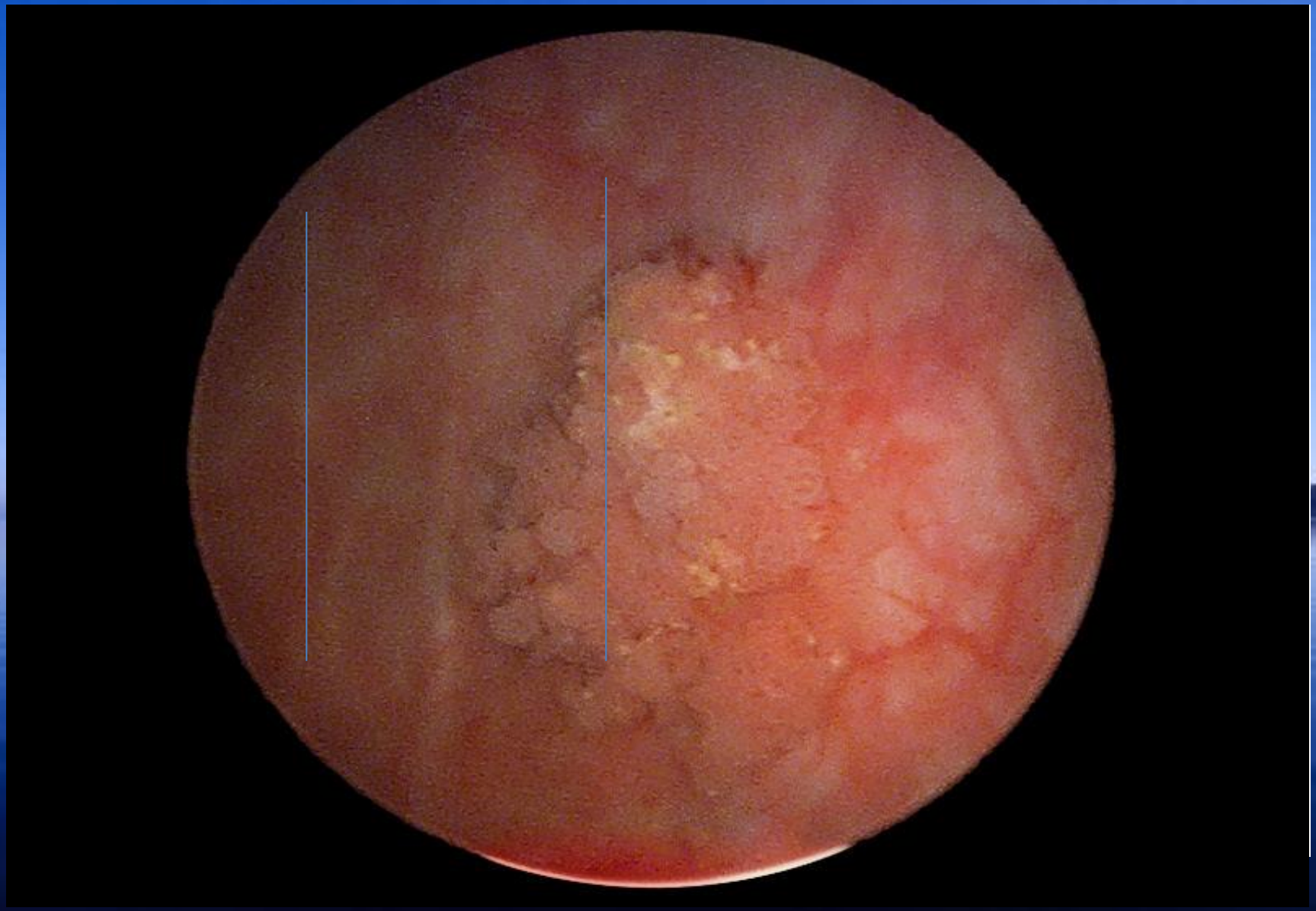

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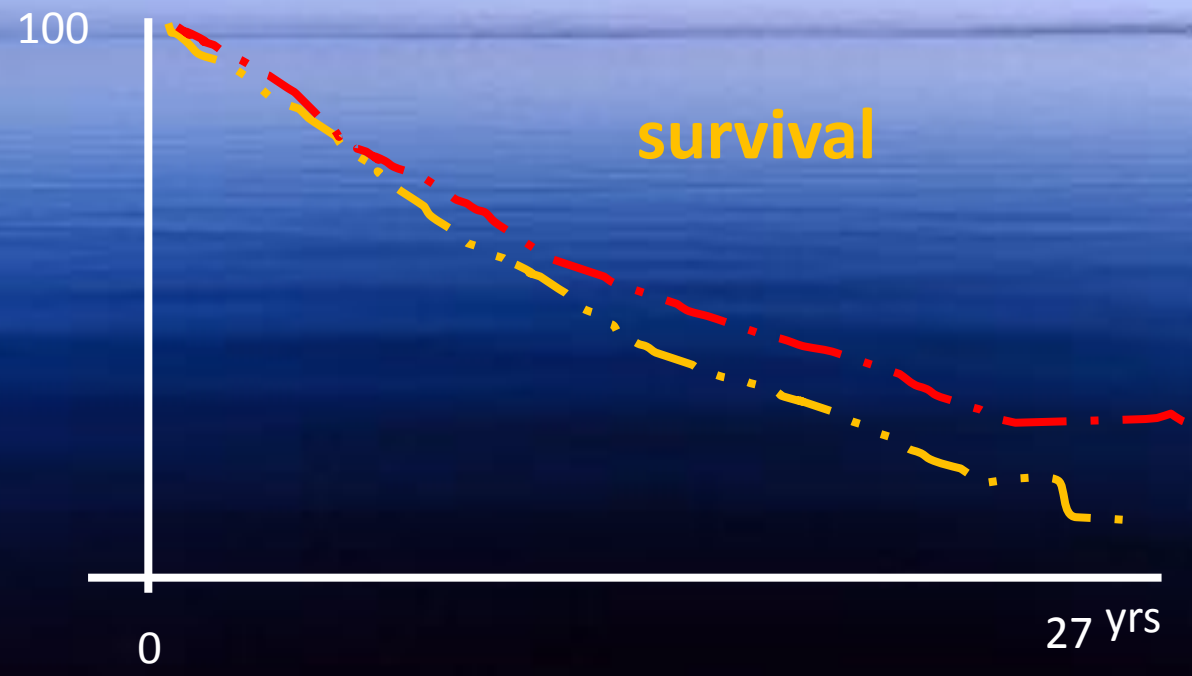
ΧΡΟΝΟΣ ΣΤΗΝ ΠΡΩΤΗ ΥΠΟΤΡΟΠΗ

EORTC RECURRENCE RISK SCORE

Single installation No installation

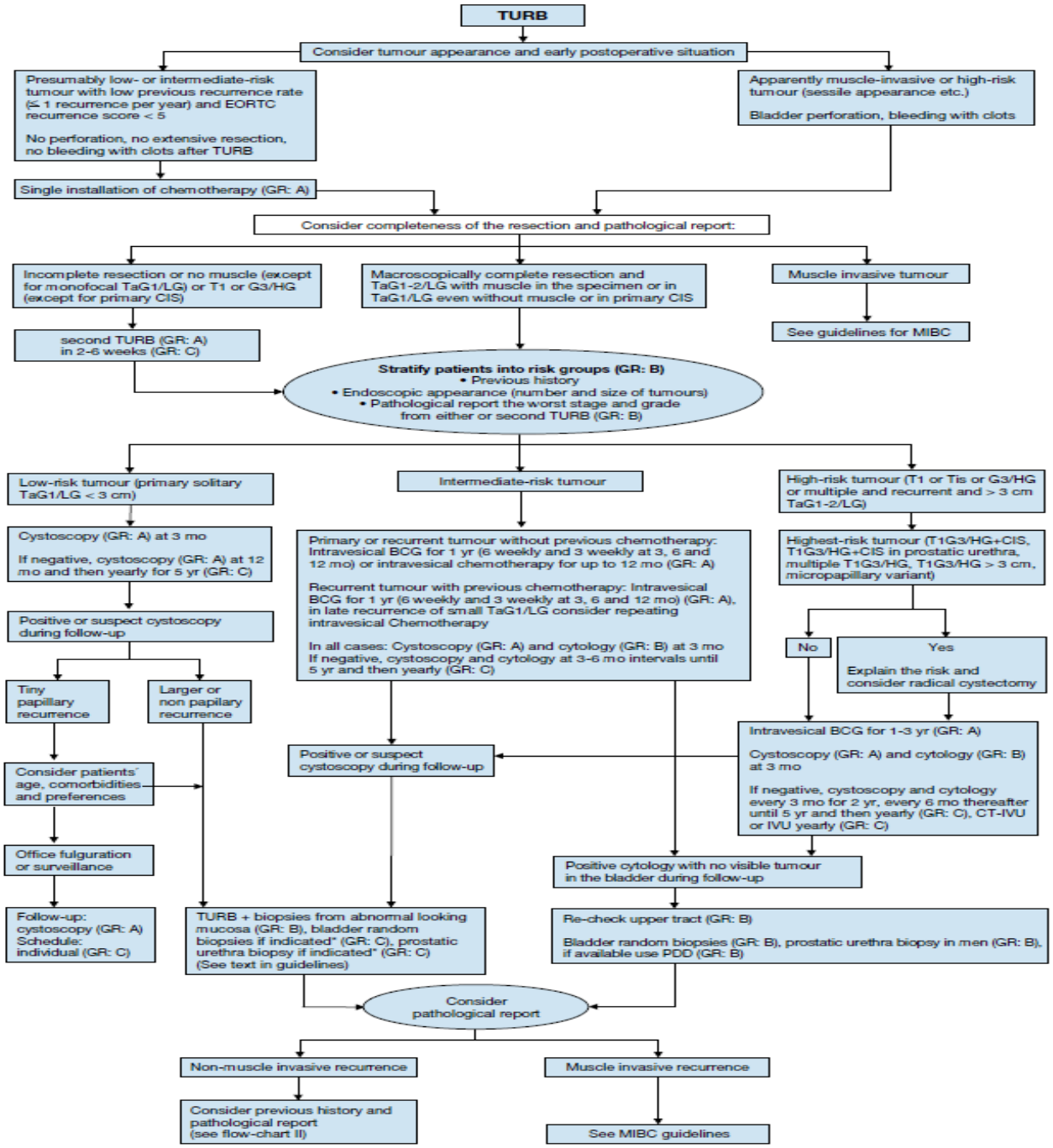

100
Time to progression
No installation
single installation
27 yrs
0


100
survival
No installation
single installation
0
27 yrs

Ποιοι θα επωφεληθούν

Ασθενείς με λιγότερο από μία υποτροπή τον χρόνο

EORTC SCORE <5


TURB
Consider tumour appearance and early postoperative situation
Presumably low- or intermediate-risk tumour with low previous recurrence rate (≤ 1 recurrence per year) and EORTC recurrence score < 5
No perforation, no extensive resection, no bleeding with clots after TURB
Apparently muscle-invasive or high-risk tumour (sessile appearance etc.)
Bladder perforation, bleeding with clots
Single installation of chemotherapy (GR: A)
Consider completeness of the resection and pathological report:
Incomplete resection or no muscle (except for monofocal TaG1/LG) or T1 or G3/HG (except for primary CIS)
Macroscopically complete resection and TaG1-2/LG with muscle in the specimen or in TaG1/LG even without muscle or in primary CIS
Muscle invasive tumour
second TURB (GR: A) in 2-6 weeks (GR: C)
See guidelines for MIBC
Stratify patients into risk groups (GR: B)
• Previous history
• Endoscopic appearance (number and size of tumours)
• Pathological report the worst stage and grade from either or second TURB (GR: B)
Low-risk tumour (primary solitary TaG1/LG < 3 cm)
Intermediate-risk tumour
High-risk tumour (T1 or Tis or G3/HG or multiple and recurrent and > 3 cm TaG1-2/LG)
Cystoscopy (GR: A) at 3 mo
If negative, cystoscopy (GR: A) at 12 mo and then yearly for 5 yr (GR: C)
Primary or recurrent tumour without previous chemotherapy: Intravesical BCG for 1 yr (6 weekly and 3 weekly at 3, 6 and 12 mo) or intravesical chemotherapy for up to 12 mo (GR: A)
Recurrent tumour with previous chemotherapy: Intravesical BCG for 1 yr (6 weekly and 3 weekly at 3, 6 and 12 mo) (GR: A), in late recurrence of small TaG1/LG consider repeating intravesical Chemotherapy
In all cases: Cystoscopy (GR: A) and cytology (GR: B) at 3 mo
If negative, cystoscopy and cytology at 3-6 mo intervals until 5 yr and then yearly (GR: C)
Highest-risk tumour (T1G3/HG+CIS, T1G3/HG+CIS in prostatic urethra, multiple T1G3/HG, T1G3/HG > 3 cm, micropapillary variant)
Positive or suspect cystoscopy during follow-up
No
Yes
Explain the risk and consider radical cystectomy
Tiny papillary recurrence
Larger or non papilary recurrence
Positive or suspect cystoscopy during follow-up
Intravesical BCG for 1-3 yr (GR: A)
Cystoscopy (GR: A) and cytology (GR: B) at 3 mo
If negative, cystoscopy and cytology every 3 mo for 2 yr, every 6 mo thereafter until 5 yr and then yearly (GR: C), CT-IVU or IVU yearly (GR: C)
Consider patients' age, comorbidities and preferences
Positive cytology with no visible tumour in the bladder during follow-up
Office fulguration or surveillance
Follow-up: cystoscopy (GR: A) Schedule: individual (GR: C)
TURB + biopsies from abnormal looking mucosa (GR: B), bladder random biopsies if indicated* (GR: C), prostatic urethra biopsy if indicated* (GR: C) (See text in guidelines)
Re-check upper tract (GR: B)
Bladder random biopsies (GR: B), prostatic urethra biopsy in men (GR: B), if available use PDD (GR: B)
Consider pathological report
Non-muscle invasive recurrence
Muscle invasive recurrence
Consider previous history and pathological report (see flow-chart II)
See MIBC guidelines


ΕΥΧΑΡΙΣΤΩ