

Contemporary management of high-grade T1 bladder cancer



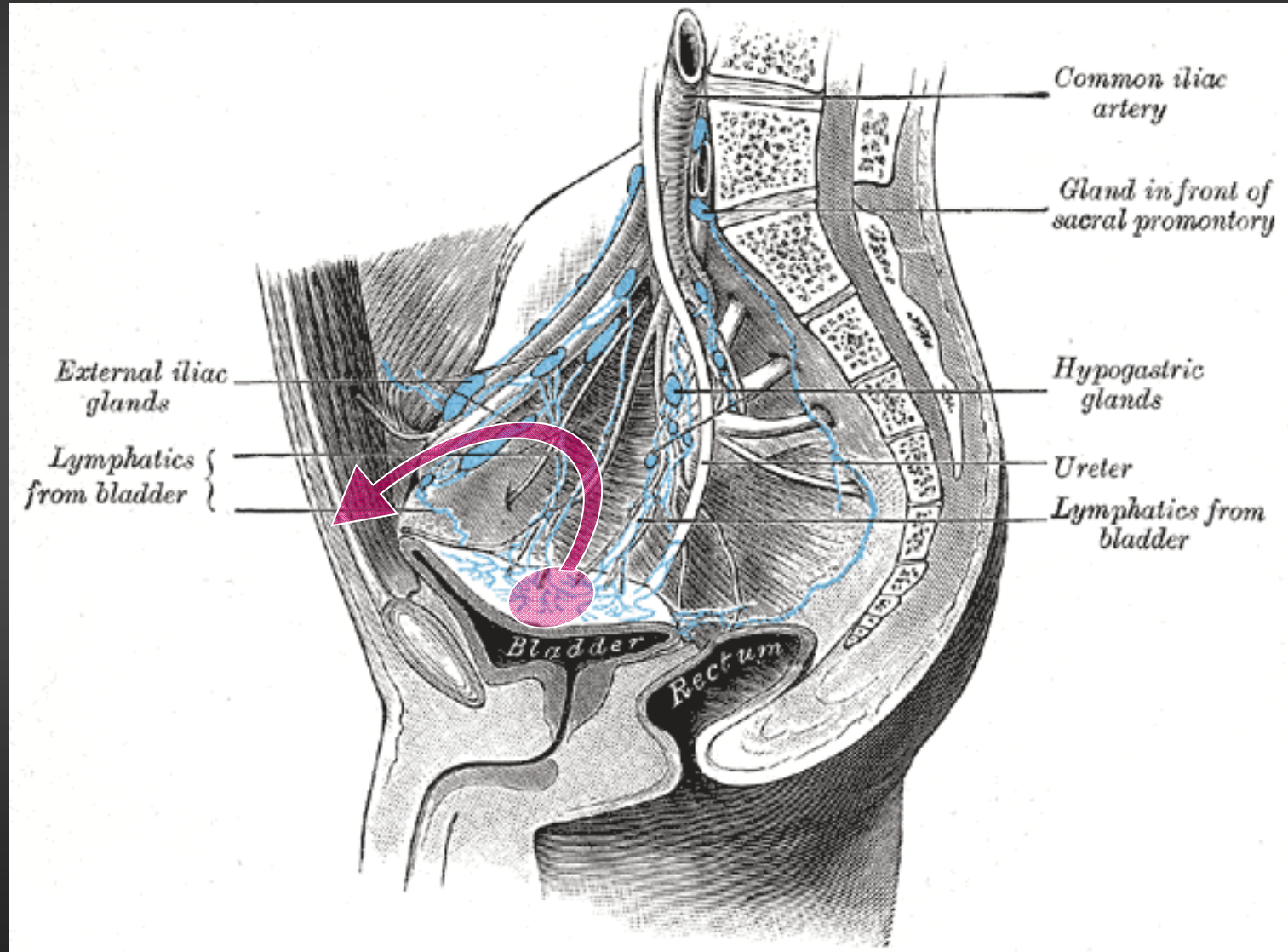
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Treatment options in HG T1 BCa

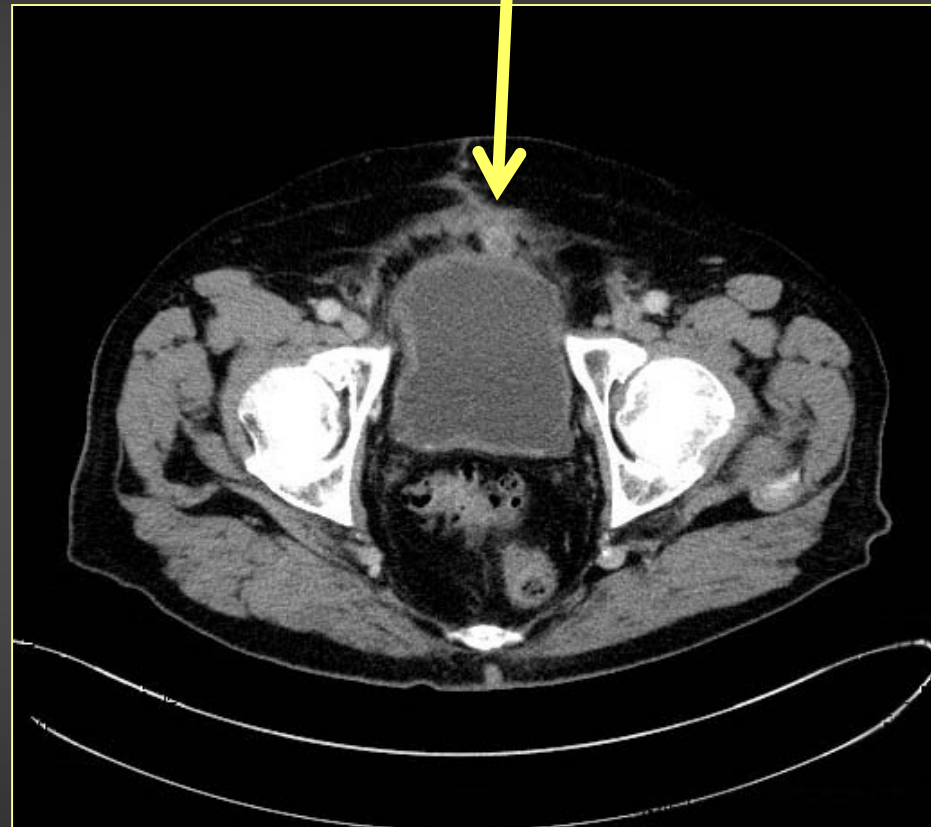
- **TUR-BT**
 - Primary and second resection (T0-status)
- **BCG-instillation vs. chemoinstillation**
 - Induction (6 course weekly)
 - Maintenance (different schedules, i.e. 6 courses 3-weekly)
- **Immediate (IRC) vs. deferred radical cystectomy (DRC)**

(open) partial cystectomy ?



T1G3 (Diverticulum)

9 months later → M1



Pathology

What we expect?

Expected information

Grade ?

Depths of tumor invasion? Substaging ?
Lymphovascular invasion ?

Lamina muscularis propria and sufficient muscle present ?

Additional pathology of biopsies (♂: prostatic urethra, ♀:
bladder neck)

The pathological report should specify the grade, depth of tumour invasion, and whether the lamina propria and sufficient muscle are present in the specimen.

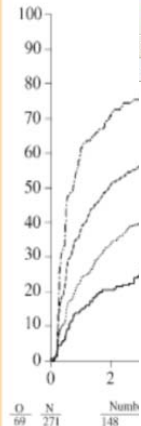
A

Risk stratification and individual tailoring of adjuvant treatment

EORTC risk tables

Table 5 - Weights used to calculate the recurrence and progression scores

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	2	3
G2	3	4
G3	4	5
Total score	0-17	0-23



Aspen think tank

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

Programmed by Richard Sylvester, EORTC Data Center, 83 avenue Mounier, 1200 Brussels, Belgium.

Version 1.0, January 2006

Not included: T1 substaging, LVI

Recurrence score	Probability of recurrence at 1 year	Probability of recurrence at 5 years	Recurrence Risk Group
0	15%	31%	Low risk
1-4	24%	46%	Intermediate risk
5-9	38%	62%	
10-17	61%	78%	High risk
Progression score	Probability of progression at 1 year	Probability of progression at 5 years	Progression Risk Group
0	0.2%	0.8%	Low risk
2-6	1%	6%	Intermediate risk
7-13			High risk
14-23	17%	45%	

Only 171 pat. treated with BCG included !

EORTC risk tables overestimate risk of progression in HG T1 BCa

EORTC risk tables

2596 pat. with HG Ta/T1 HG Bca
7 randomized trials
Only 171 pat. with BCG (6.6%)

Validation
study

CUETO (Spanish)

1062 patients with HG Ta/T1 HG
randomized trials
BCG over 5-6 months in all

PSEP:

P(worst) - P(best)

Leg: P(worst)/P(best):

Predicted probability in
group with worst/best
prognosis

„The greater the difference,
the better the discrimination
between two individuals with
different outcomes“

Table 3 – Prognostic separation index (PSEP) values for recurrence and progression in the European Organization for Research and Treatment of Cancer (EORTC) and Club Urológico Español de Tratamiento Oncológico (CUETO) series at 1 yr and 5 yr

	PSEP at 1 yr		PSEP at 5 yr	
	EORTC	CUETO	EORTC	CUETO
Recurrence (1)*	0.46	0.3	0.47	0.49
Recurrence (2)*		0.26		0.51
Progression	0.168	0.105	0.42	0.25

* Recurrence (1): All recurrent tumors were considered as having no more than one recurrence per year. Recurrence (2): All recurrent tumors were considered as having more than one recurrence per year.

$\Delta=0.02$

$\Delta=0.17!$

The high PSEP for progression suggested by the EORTC do not apply for contemporary BCG series !

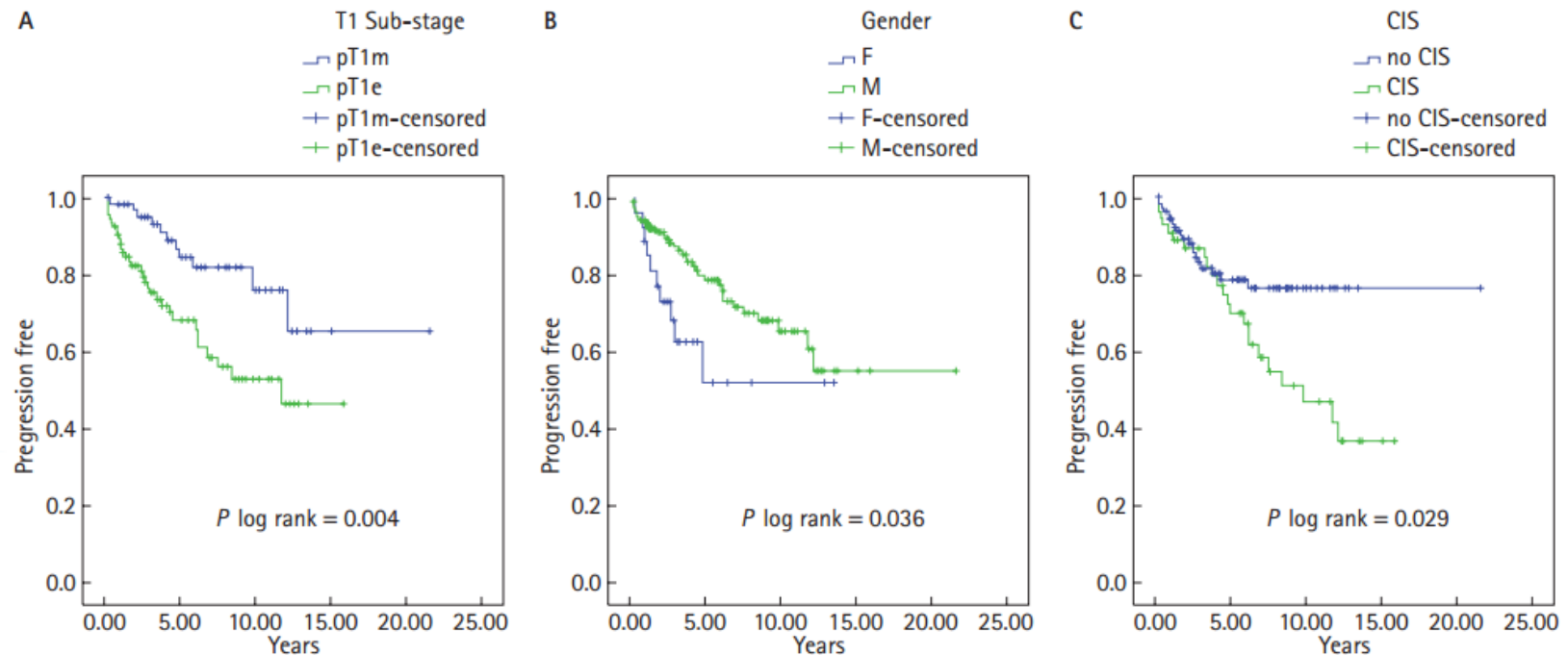
Risk factors for progression in HG T1 BCa

Substaging

Gender

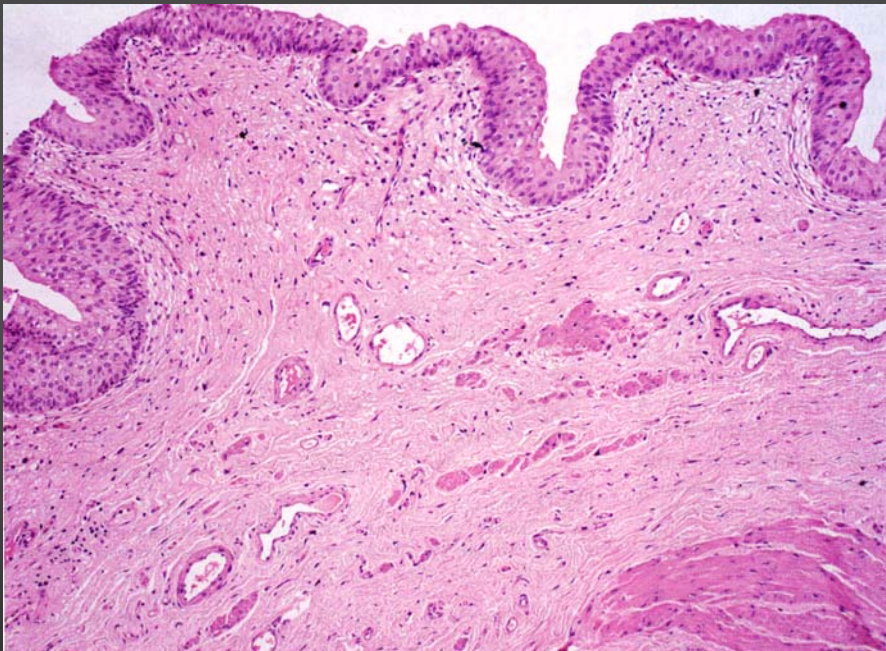
Cis

FIG. 3. Kaplan–Meier curves for **A**, sub-stage (T1m/T1e; P log-rank = 0.004); **B**, gender (P log-rank = 0.036); and **C**, CIS (P log-rank = 0.029).



Types of T1 substaging

Substaging
infiltration depth in
mm

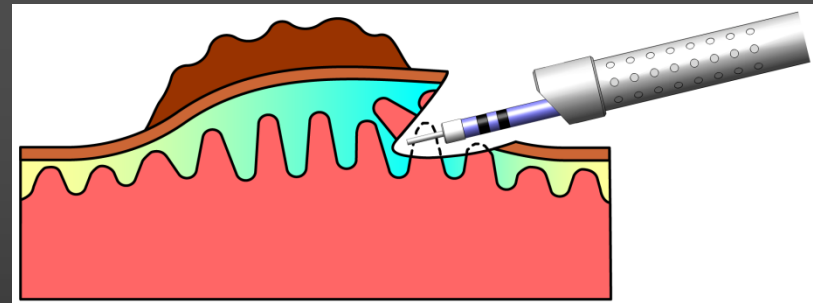
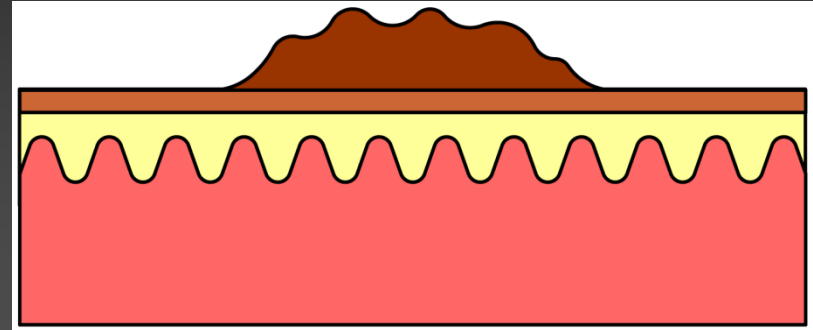
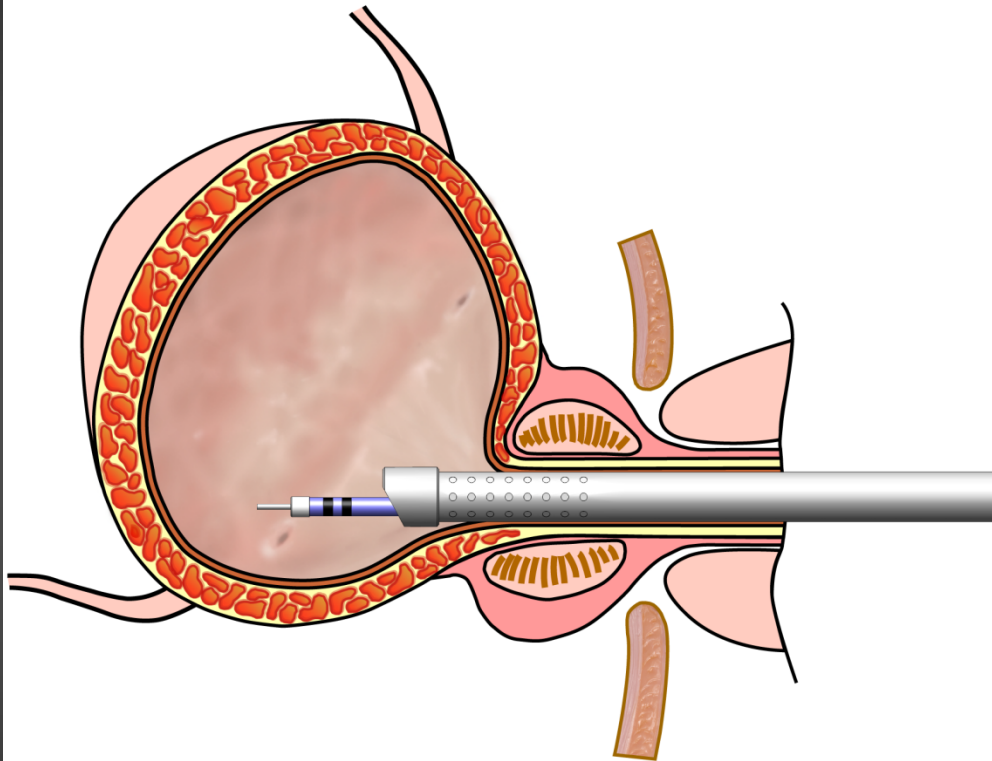


Zhou, Magi-Galluzi, Genitourinary Pathology, Foundations in Diagnostic Pathology, Elsevier

Substaging
according to anatomical
landmark



Peacemeal vs in toto resection - Hybrid knife ?



LVI- independent risk factor for progression

TABLE 2 Comparative risk factors for recurrence/progression across the decades

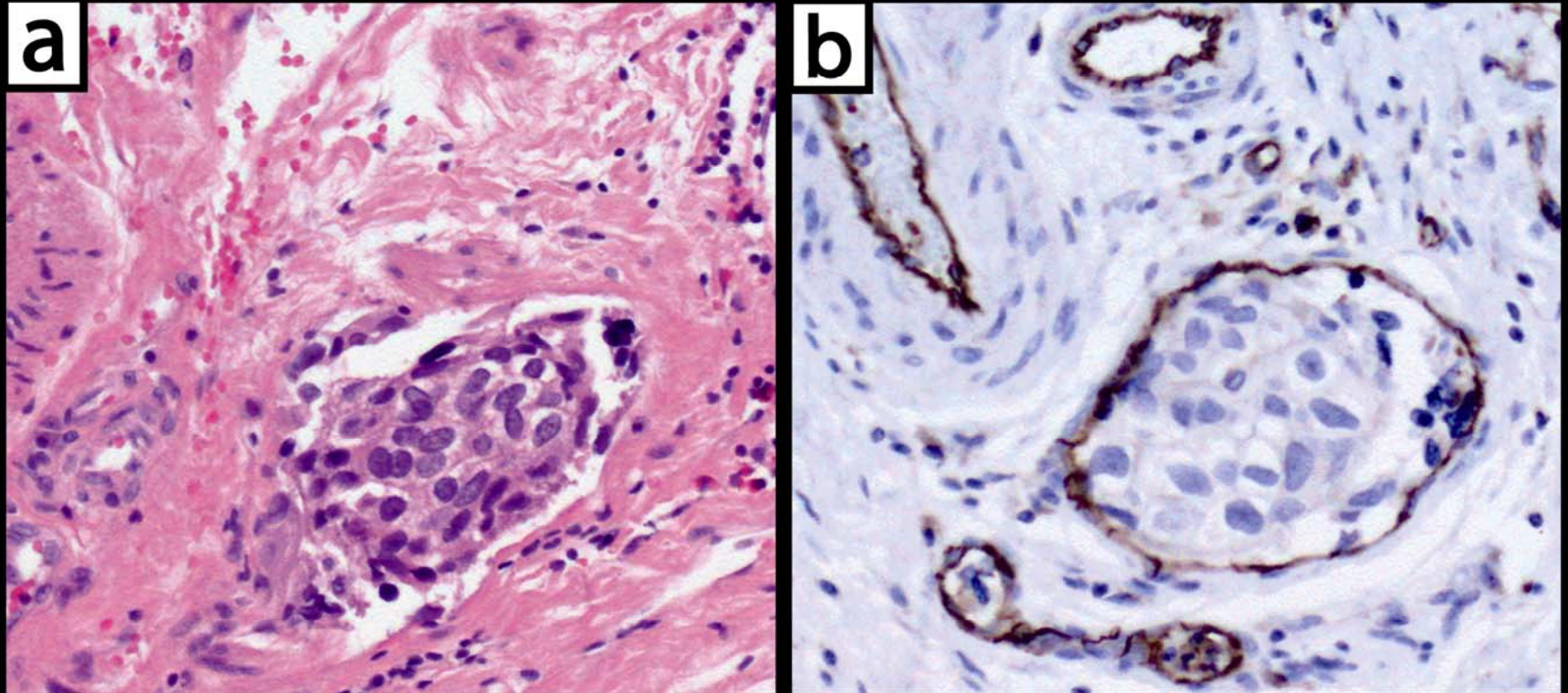
	1990–1999			2000–2010		
	IRC	CM	P value	IRC	CM	P value
Total cohort	54	36		59	200	
Prostatic urethral involvement (%)	3/54 (5.6)	3/36 (8.3)	0.605	5/59	13/200	0.600
Bladder neck involvement (%)	10/54 (18.5)	5/36 (13.9)	0.564	10/54 (18.5)	5/36 (13.9)	0.564
Carcinoma <i>in situ</i> (%)	20/54 (37.0)	11/36 (30.1)	0.526	15/59 (25.4)	56/200 (28.0)	0.697
LVI (%)	14/54 (25.9)	8/36 (22.2)	0.689	13/59 (22.0)	13/200 (6.5)	<0.001
Presence of muscularis propria (%)			<u>0.001</u>			<u>0.104</u>
No	32/54 (59.3)	10/36 (27.8)		26/59 (44.1)	87/200 (43.5)	
Yes	17/54 (31.5)	11/36 (30.6)		28/59 (47.5)	74/200 (19.5)	
Unknown	5/54 (9.3)	15/36 (41.7)		5/59 (8.5)	39/200 (19.5)	

N=349 pat., HG T1, IRC: defined as within 90days after diagnosis
Columbia University, New York, USA

Badalato et al, BJU Int, 2012

LVI- conventional vs. immunohistochemical staining

34 high risk T1 pat. treated with IRC vs. DRC

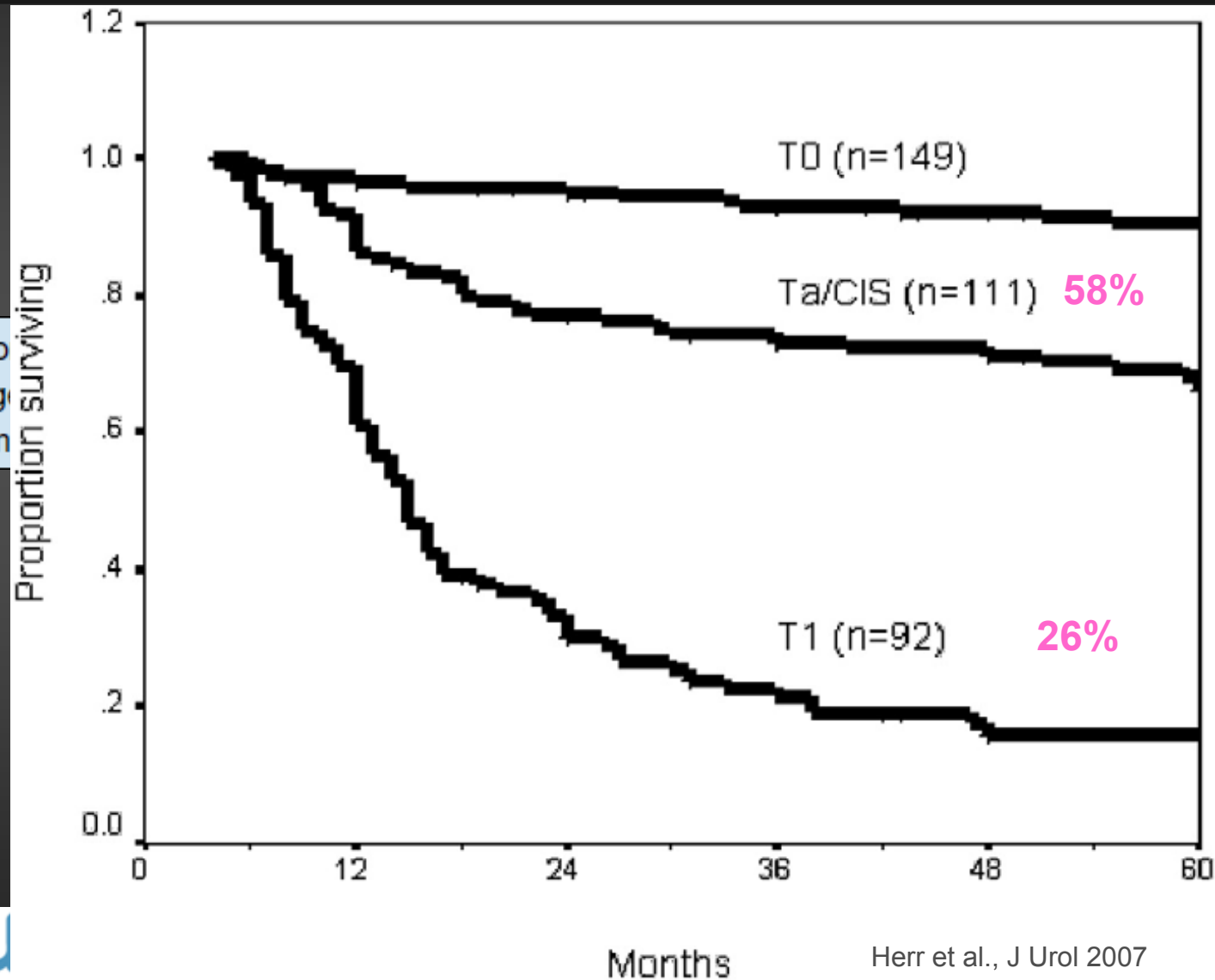


Improved detection rate of LVI by IHC at primary TUR-BT



Patients with LVI at highest risk of progression

Re-TUR in all HG T1 Bca?

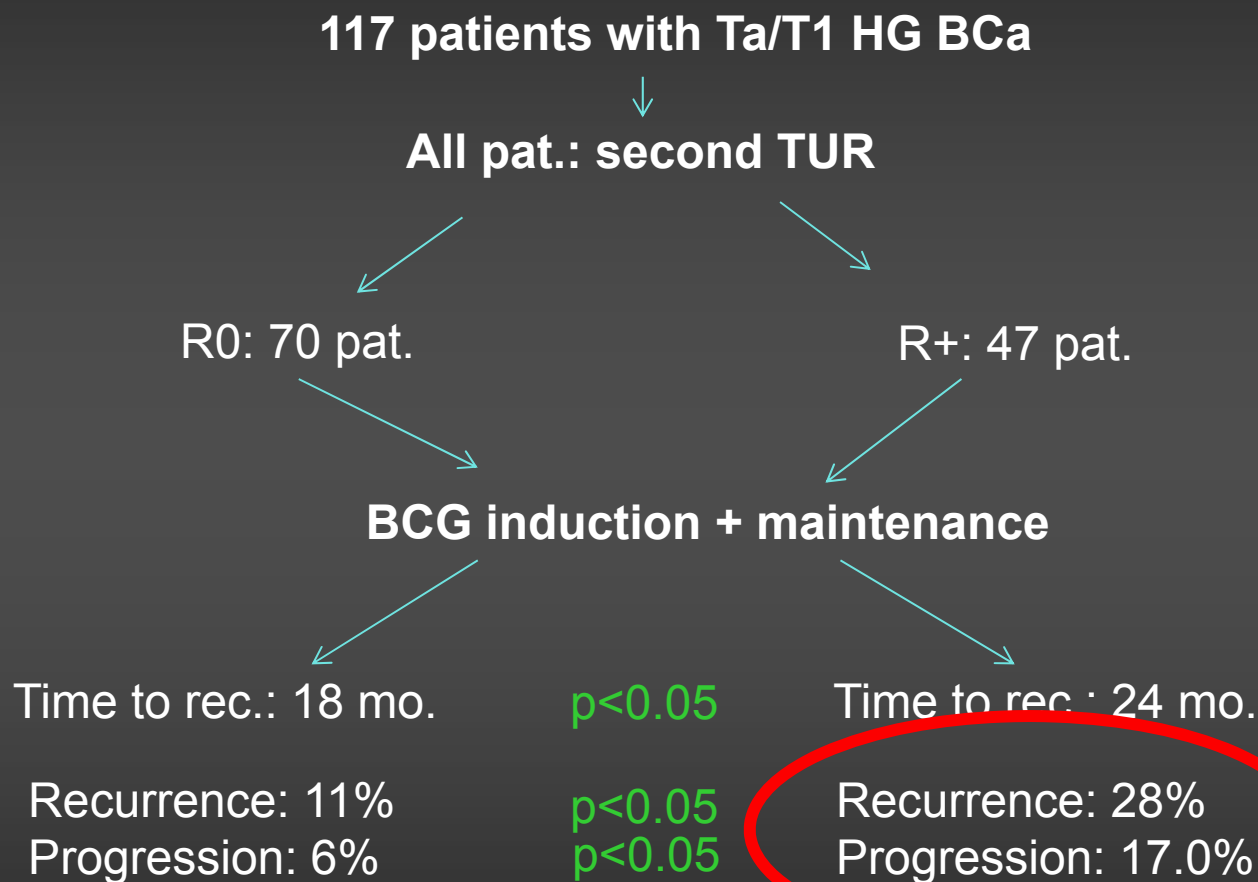


A second
(in large
T1 tum

complete
e and/or

A

T0 status before BCG



→ Recurrences more likely to be LG tumors in tumor-free pat. !

BCG vs. epirubicin/IFN2b in HGT1 BCa

Nordic multicenter, prospective, randomized trial
250 patients with T1 G2-3 BCa
All pat.: second TUR

↓
Primary endpoint: RFS

BCG

Induction: 6 weeks
Maintenance: 2 yrs

Epirubicin/IFN2b

At F/U: 24 mo. RFS: 73%

$p=0.01$

RFS: 62%

Multivariable Tumor size

Multiplicity, grade,
status at second TUR

Superiority of BCG mainly in those HG T1 with concomitant Cis

Feasibility of chemoinstillation in HG T1 at modest risk of progression

BCG-maintenance essential for superiority to chemoinstillation

Recurrence and Progression in T1G3 BCa in the BCG era

Recurrence

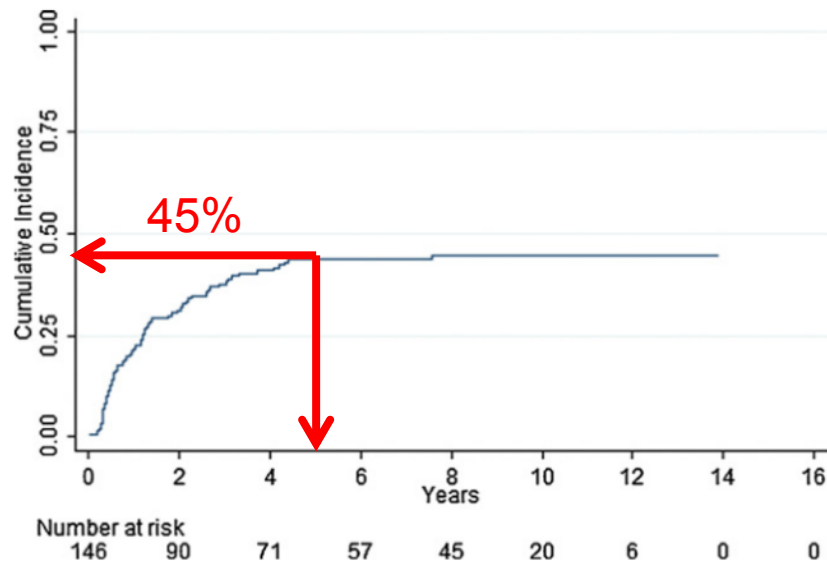


Fig. 1 – Cumulative incidence curve of time to first recurrence (all patients).

Progression

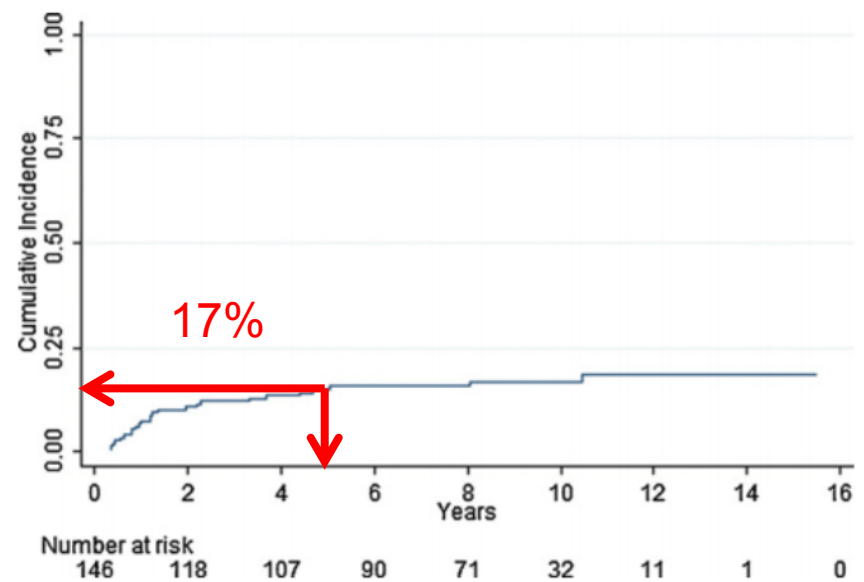


Fig. 3 – Cumulative incidence curve of time to progression (all patients).

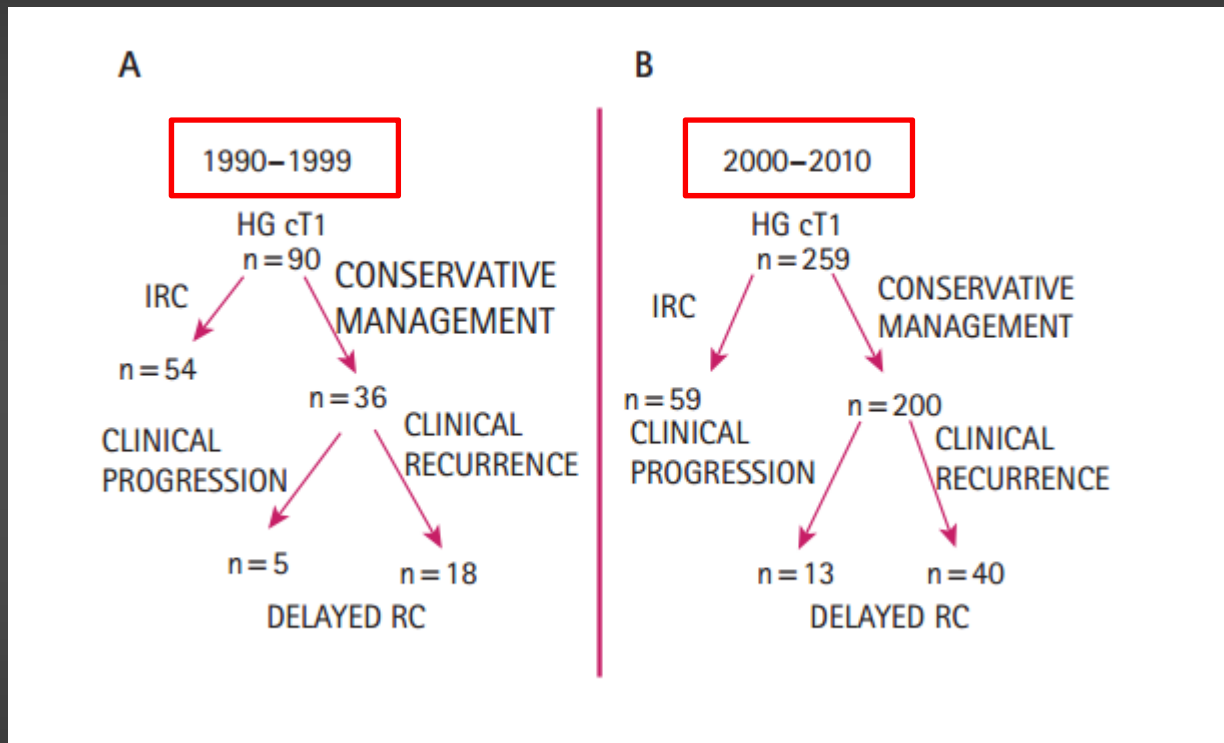
N=146 pat.

Concom. Cis: 65%

TUR-BT+ induction BCG (81mg Connaught) w/o maintenance

median F/U: 8.7 yrs

Immediate Cystectomy in HGT1 BCa in the last 20 years



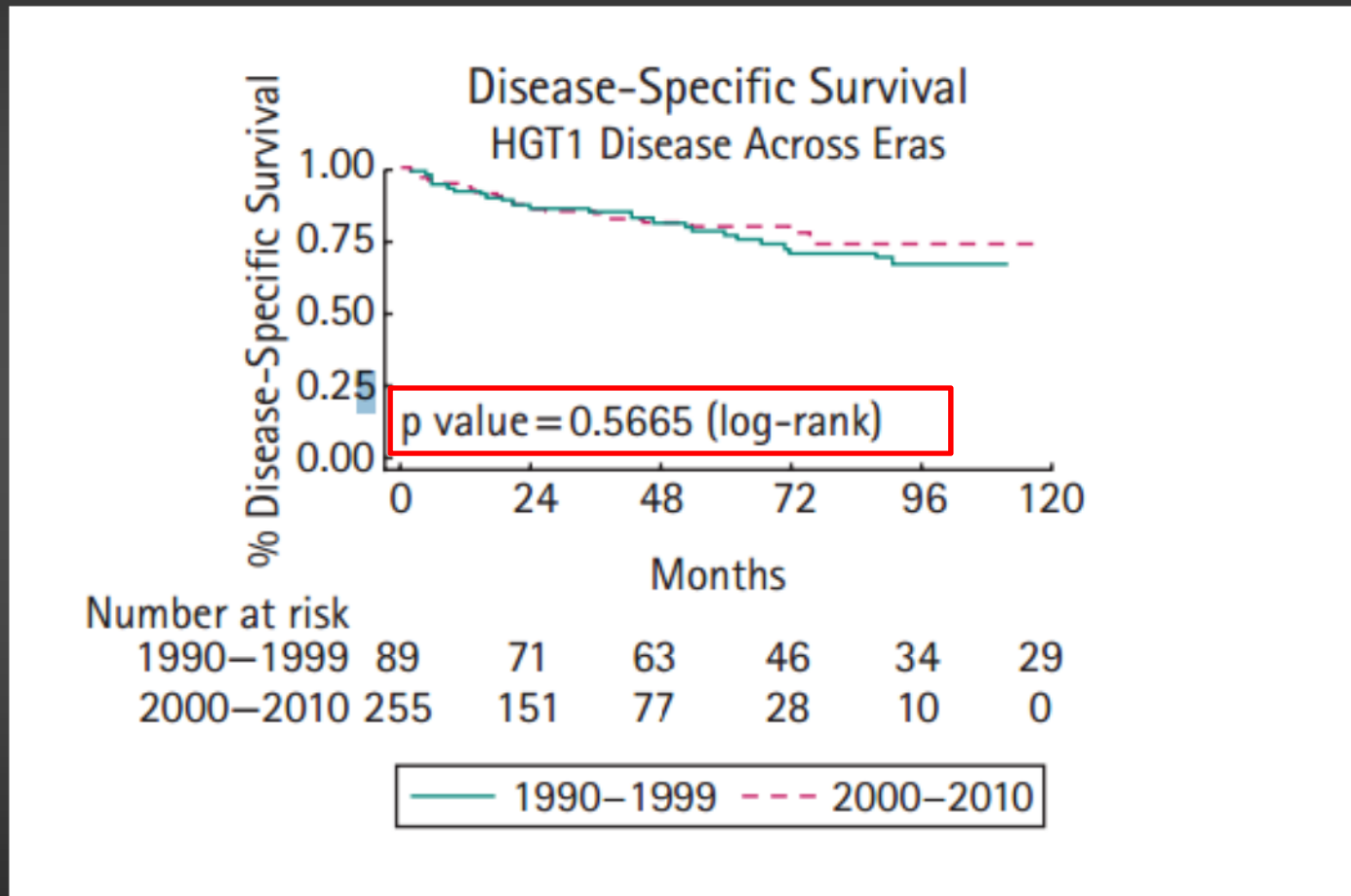
1990-1999:
IRC: 60%



2000-2010
IRC: 23%

IRC vs. bladder preservation

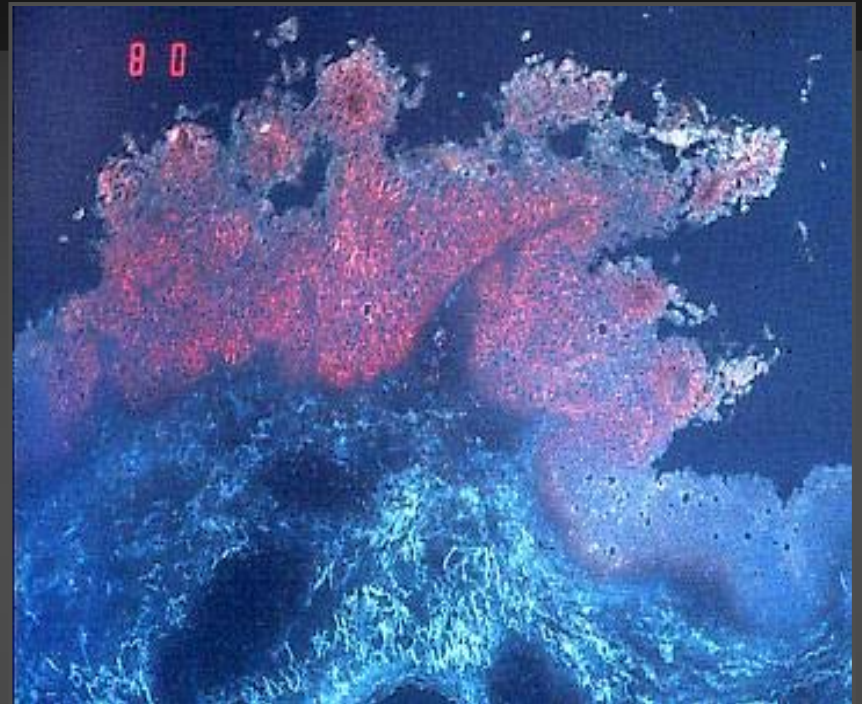
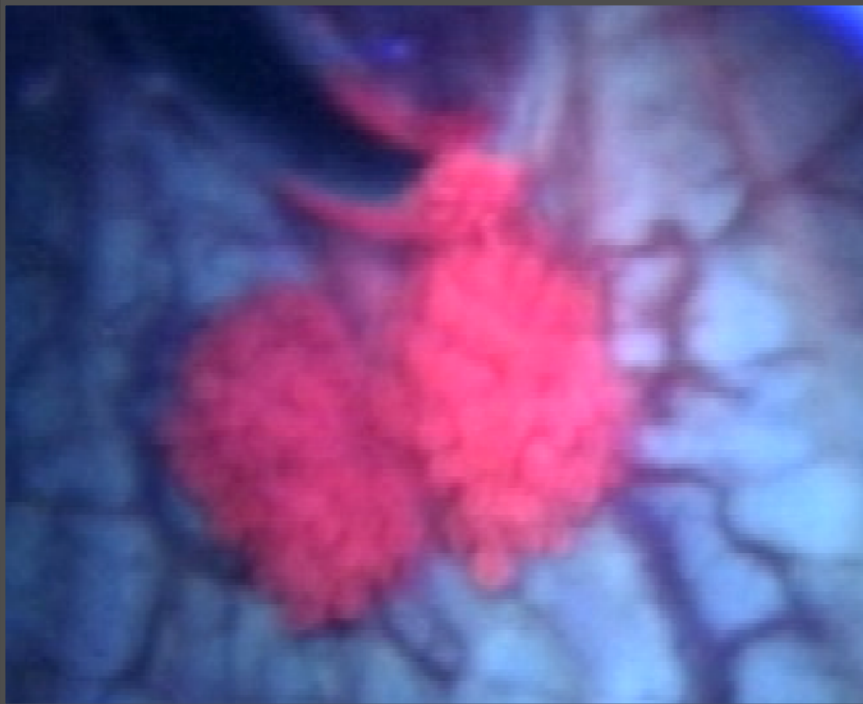
Survival across eras



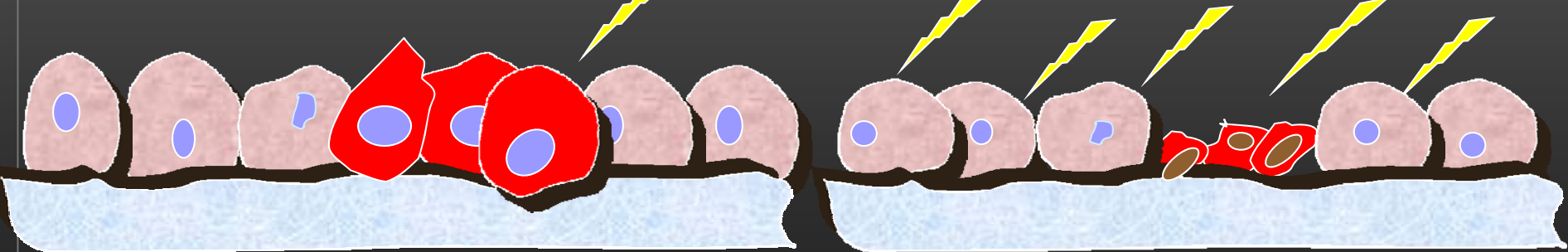
N=349 pat., HG T1, IRC: defined as within 90days after diagnosis
Columbia University, New York, USA

Badalato et al, BJU Int, 2012

PDD - presence or absence of CIS



CIS + Peritumoral CIS



Long-Term Dec Hexaminolevuli

Van Rhijn et al, BJU Int, 2012

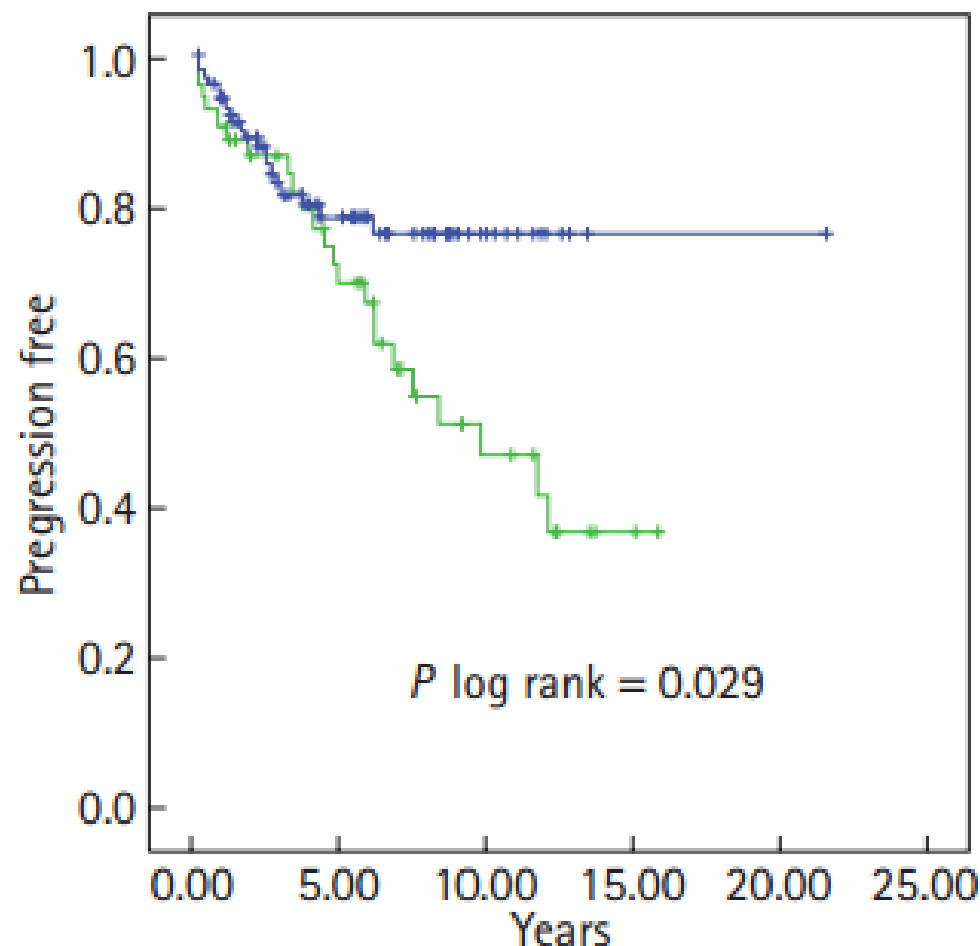
CIS

no CIS

CIS

no CIS-censored

CIS-censored



p = 0.04

p = 0.04

p = 0.14

p = 0.066

p = 0.16

enzl et al, J Urol 2012

- ITT - RFS
- PPS - RFS
- Tumor free
- T2 - T4
- Cystectomy

Conclusion

- Better tumor resection
 - Complete eradication
 - Improved staging
 - CIS +/-
- RC with resistant/refractory BCG
- BCG/alternate instillation with relapsing
- No reliable biomarkers
- No systemic Chx

ICUD Guidelines 2012

Recommendation	Level of evidence	Grade of recommendation
The prognosis of T1 urothelial carcinoma should be based on tumor grade, early recurrence, multiplicity, tumor size, concomitant CIS, urothelial carcinoma involving the prostate, and depth of lamina propria invasion.	1a	A
High-risk patients and patients with recurrent or persisting disease after BCG should be offered a cystectomy.	2a	A
If a bladder-sparing approach is desired, a secondary TURBT should be performed and followed by intravesical BCG therapy.	3	B
CIS = carcinoma in situ; BCG = bacillus Calmette-Guérin; TURBT = transurethral resection of bladder tumor.		

Recommendation	Level of evidence	Grade of recommendation
The threat of progression remains real but comfortably low enough within the first 6 mo of initiating BCG to consider alternatives to cystectomy for those patients unfit or unwilling to undergo this standard management option.	2b	B
Failure to achieve a complete response to BCG is an indication for cystectomy.	2a	A
The current best option for BCG-resistant disease (persistence 3 mo after induction cycle) and BCG-relapsing disease (recurrence after disease-free interval of 6 mo) is repeat TURBT and BCG.	1b	A
Gemcitabine and thermochemotherapy have shown efficacy, but more studies are needed. There is no reported evidence of significant efficacy using current intravesical chemotherapy, interferon- α monotherapy, photodynamic therapy, or radiation therapy.	4	C
BCG = bacillus Calmette-Guérin; TURBT = transurethral resection of bladder tumor.		