Case description

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  - Arterial hypertension
  - Former smoker (40 pack years)
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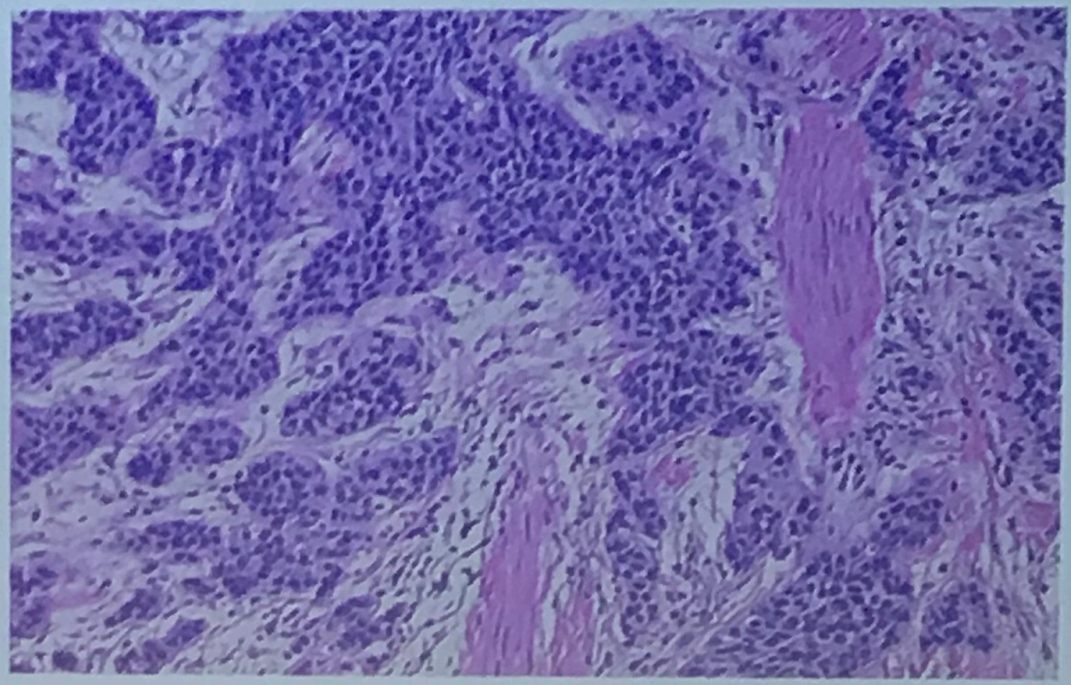
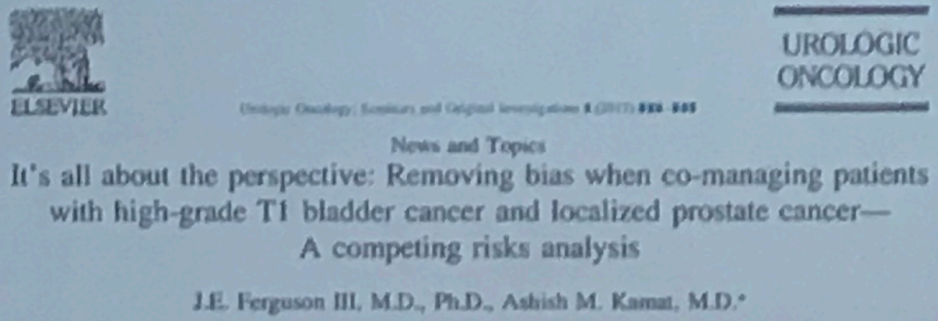
  - TURBT shows pTa high grade
- He would like to keep his bladder if possible

Should he have undergone RC in the 1st place?

- T1HG is not a superficial cancer



T1 HG is potentially lethal



T1 HG = cT3b
Gleason 5+5
12/12 positive cores
PSA 75 ng/ml

T1 HG is a high risk cancer

Primary Treatment Outcomes

+	PROBABILITY OF CANCER-SPECIFIC SURVIVAL AFTER RADICAL PROSTATECTOMY	10 YR 86% 15 YR 67%
+	PROGRESSION-FREE PROBABILITY AFTER RADICAL PROSTATECTOMY	5 YR 3% 10 YR 2%

Memorial Sloan Kettering Cancer Center

Based on Your Information Edit Information

Disqualifying Treatments	
Hormone Therapy	No
Radiation Therapy	No
General Information	
Age	70 years
Pretreatment PSA	75 ng/mL
Gleason Pattern	
Primary Gleason at biopsy	Pattern 5
Secondary Gleason at biopsy	Pattern 5
Biopsy Gleason score	10
Clinical Tumor Stages	
Clinical Tumor Stage (AJCC Version 7, 2010)	T3b
Biopsy Cores	
Number of positive biopsy cores	12 cores
Percentage of positive biopsy cores	100.00%

Survival benefit of CE for pT1 HG

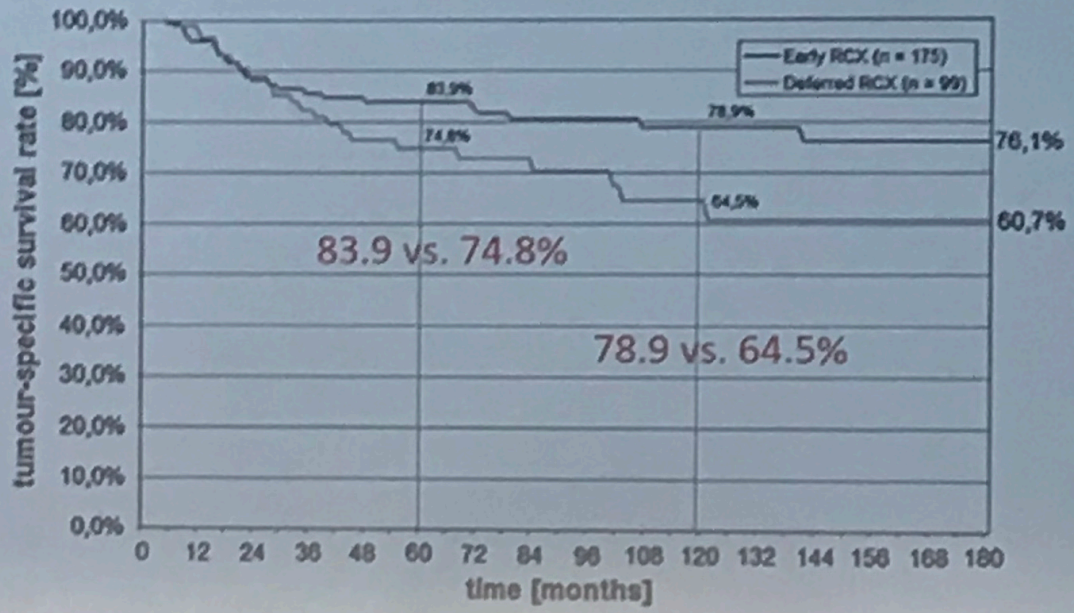
World J Urol (2009) 27:347–351
DOI 10.1007/s00345-009-0402-4

TOPIC PAPER

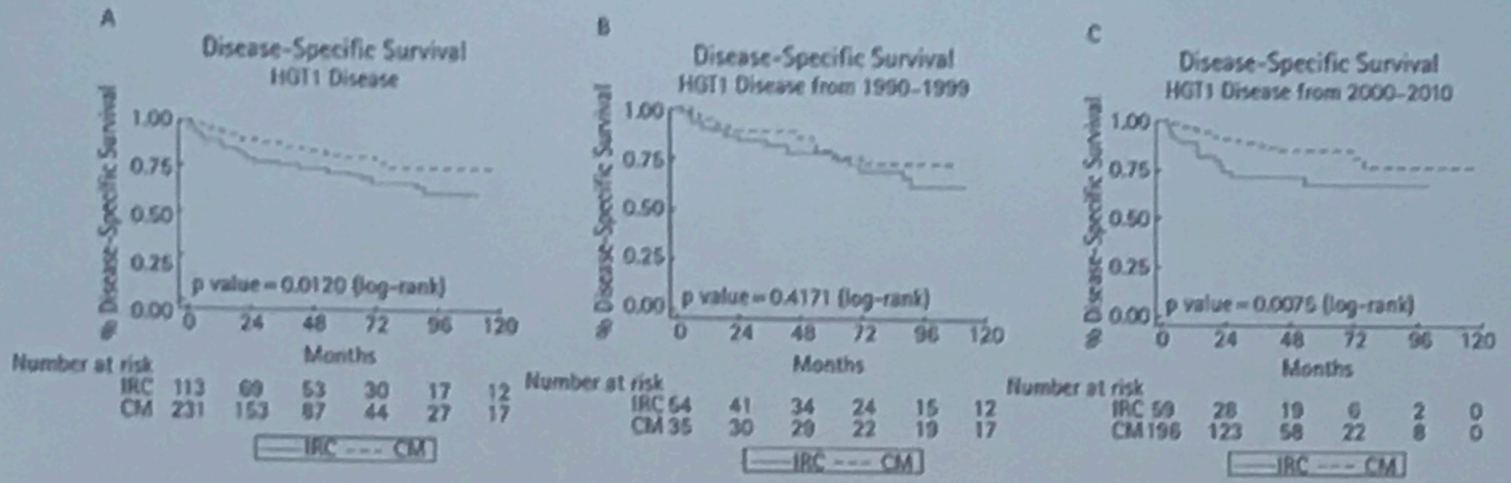
Quantification of the survival benefit of early versus deferred cystectomy in high-risk non-muscle invasive bladder cancer (T1 G3)

Richard E. Hautmann · Bjoern G. Volkmer · Kilian Gust

	Early RCX	Deferred RCX	Early RCX (%)	Deferred RCX (%)
NMIBC	124	36	70.9	36.4
Organ-confined	20	29	11.4	29.3
Not organ-confined	15	14	8.6	14.1
Lymph node positive	16	20	9.1	20.2
Total	175	99		



Immediate CE vs. BCG



	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 *in situ* (%)	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

Badalato et al. BJU Int. 2012 Nov;110(10):1471-7.

Is TURBT understaging HR NMIBC?

eau
European Association of Urology

Collaborative Review – Bladder Cancer

An Updated Critical Analysis of the Treatment Strategy for Newly Diagnosed High-grade T1 (Previously T1G3) Bladder Cancer

Girish S. Kulkarni[a,], Oliver W. Hakenberg[b], Juergen E. Gschwend[c], George Thalmann[d], Wassim Kassouf[e], Ashish Kamat[f], Alexandre Zlotta[g]*

Table 2 – Contemporary outcomes of T1G3 bladder cancer managed with immediate or early radical cystectomy

Study	Time frame	*n*	Upstaging, %	LN positive, %	Recurrence, %#	DSS*, %	OS#, %
Herr and Sogani [56]*	1979–1984	35	NR	NR	NR	92	NR
Dutta et al [7]*	1995–1999	78	40	12	NR	78	64
Thalmann et al [80]	1980–1999	29	41	14	21	69	54
Masood et al [81]	1992–2002	30	27	NR	NR	88	NR
Bianco et al [82]	1990–2000	66	27	9	78	78	NR
Lambert et al [58]	1990–2005	104	40	NR	48	93	87
Gupta et al [83]	1984–2003	167	50	18	29	82	69
Denzinger et al [57]	1995–2005	54	26	NR	NR	78	NR

Case description

- Man, 65 years old
  - Arterial hypertension
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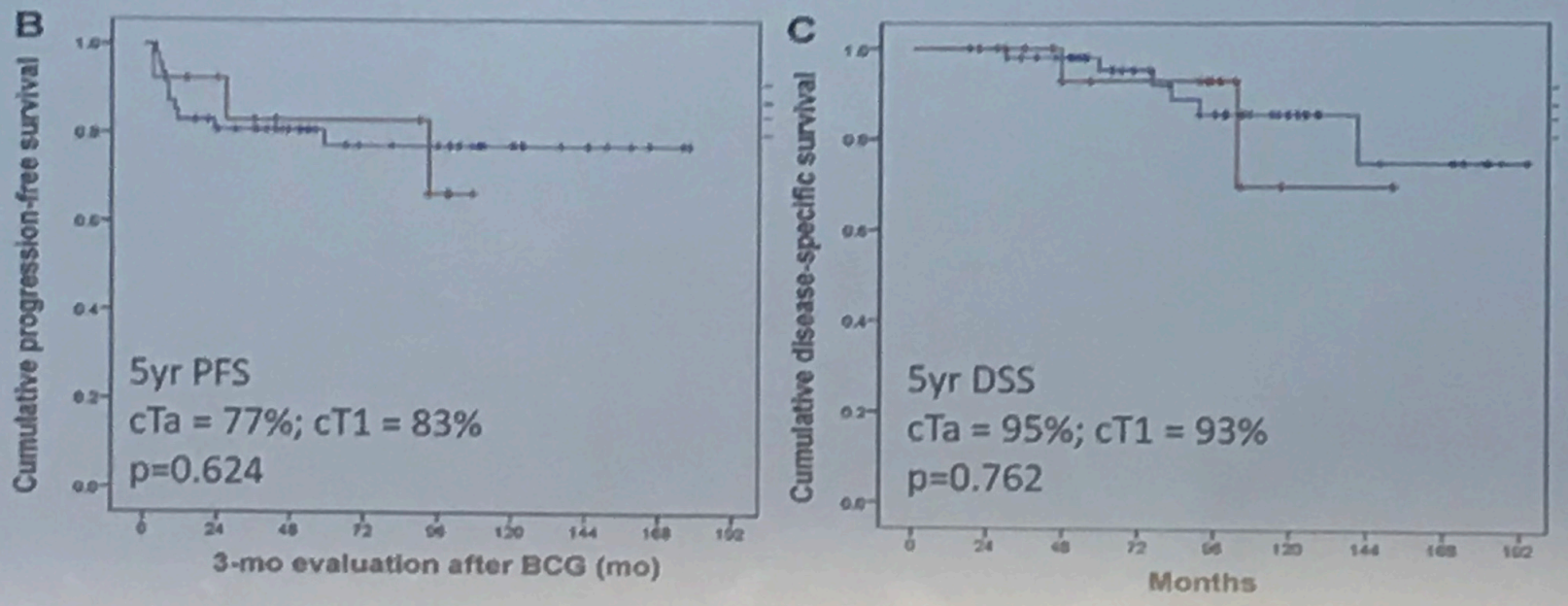
  - TURBT shows pTa high grade
- He would like to keep his bladder if possible

Recurrence of tumor

Papillary Recurrence of Bladder Cancer at First Evaluation after Induction Bacillus Calmette-Guérin Therapy: Implication for Clinical Trial Design

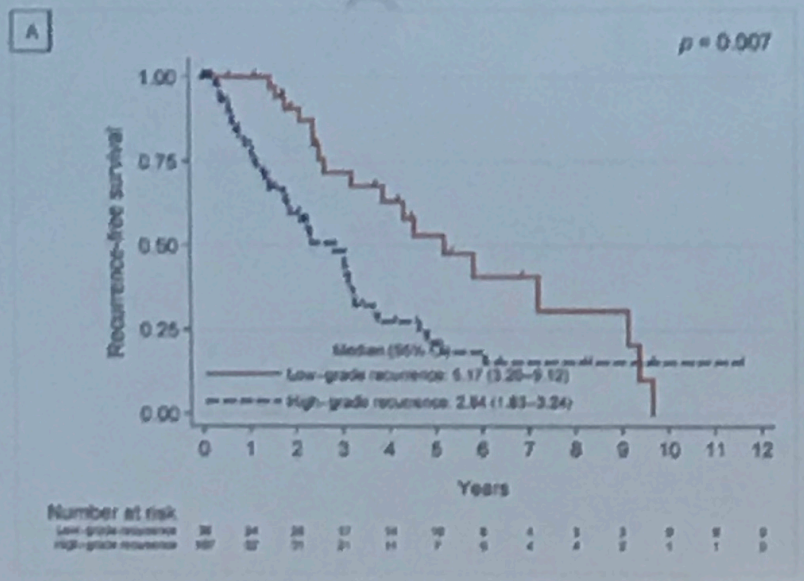
Chinedu O. Mmeje[a], Charles C. Guo[b], Jay B. Shah[c], Neema Naval[a], H. Barton Grossman[a], Colin P. Dinney[a], Ashish M. Kamat[a,]*

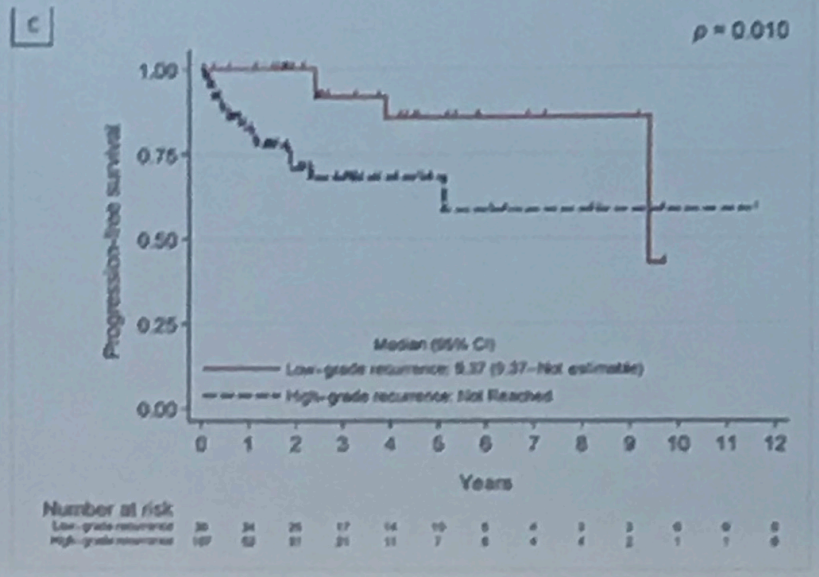


What is the risk based on grading?

European Association of Urology

Using Grade of Recurrent Tumor to Guide Further Therapy While on Bacillus Calmette-Guerin: Low-grade Recurrences Are not Benign





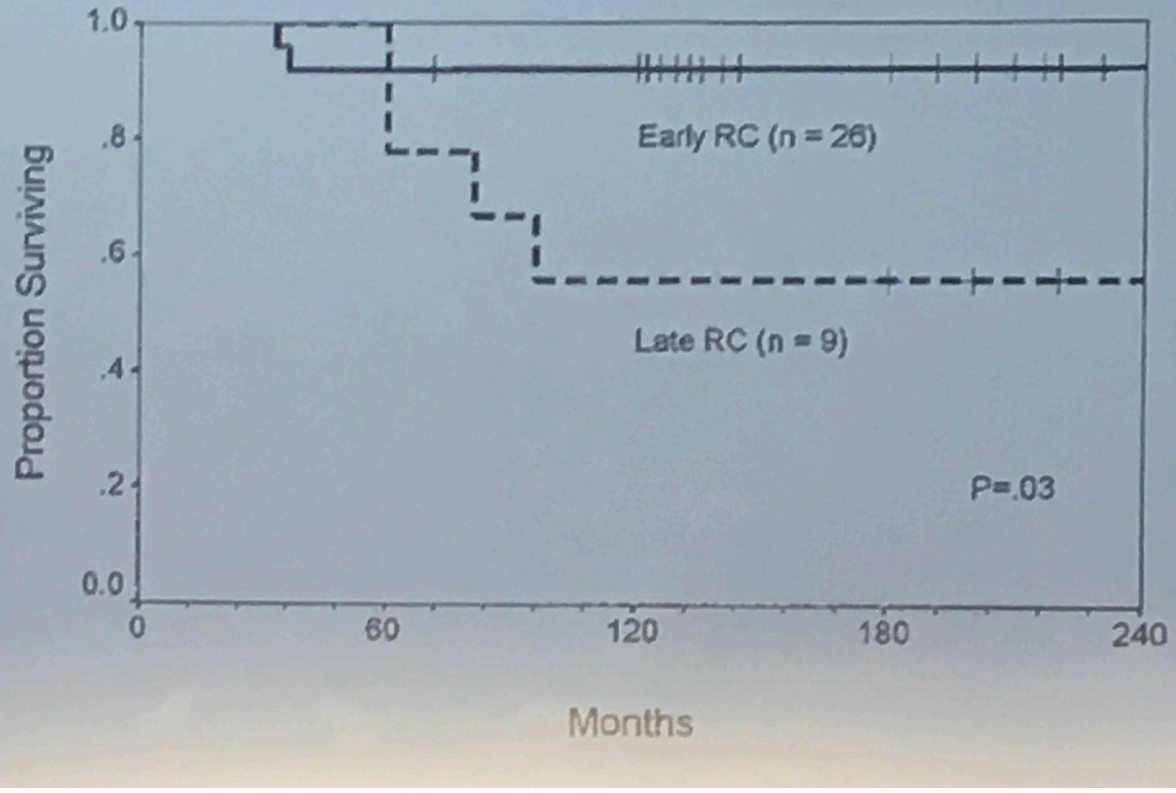
Recurrent HG disease after BCG

DOES EARLY CYSTECTOMY IMPROVE THE SURVIVAL OF PATIENTS WITH HIGH RISK SUPERFICIAL BLADDER TUMORS?

HARRY W. HERR AND PRAMOD C. SOGANI

From the Department of Urology, Memorial Sloan Kettering Cancer Center, New York, New York

"Of 35 patients with recurrent superficial bladder tumors 92% and 56% survived who underwent cystectomy less than 2 years after initial BCG therapy and after 2 years of followup, respectively."

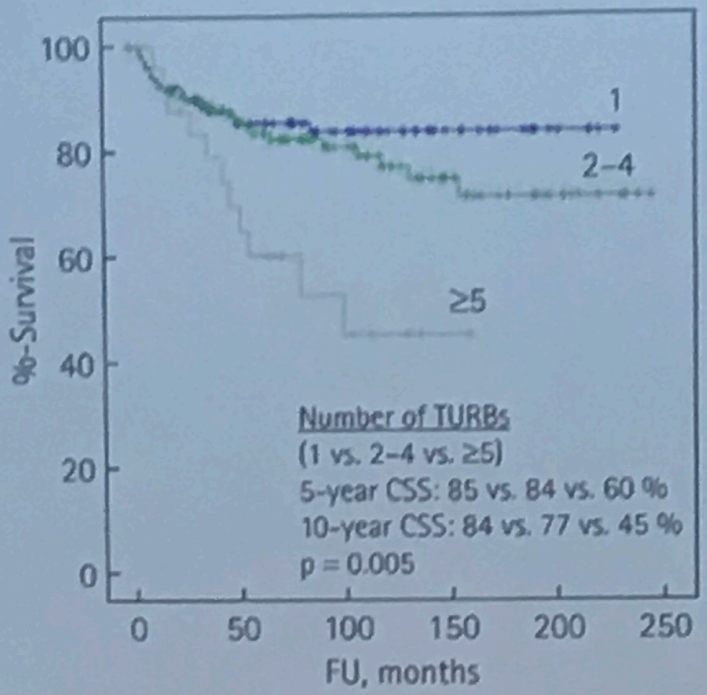


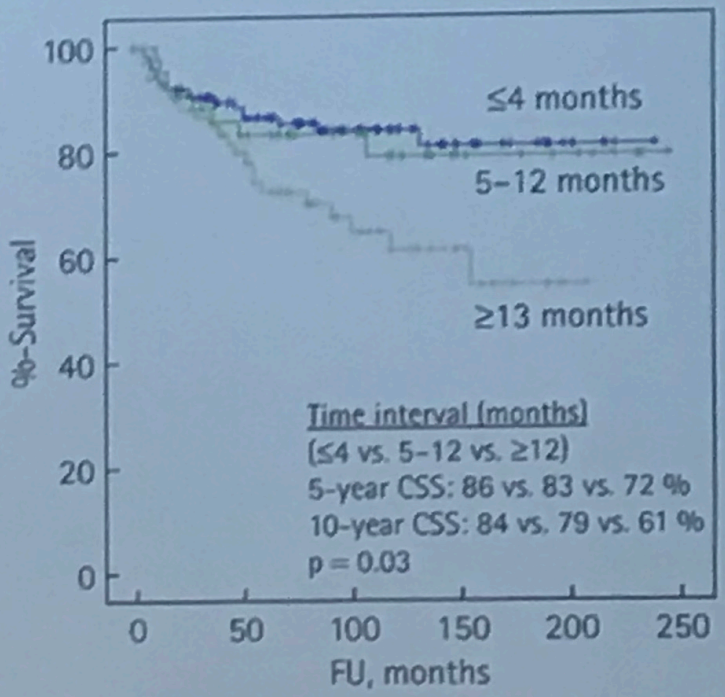
Timing of radical cystectomy

BJUI

Early vs delayed radical cystectomy for 'high-risk' carcinoma not invading bladder muscle: delay of cystectomy reduces cancer-specific survival

Wolfgang Jäger, Christian Thomas, Silke Haag, Christian Hampel, Alice Salzer, Joachim W. Thüroff and Christoph Wiesner





Multivariate analysis identified independent risk factors for CSS:

- number of TURBs (HR, 0.14,p < 0.001),
- interval between first TURB and rCx (HR, 3.27;p= 0.017)

BCG failure rates

- **BCG fails in up to 50% of patients** (4yr follow-up)
  - about half of them within the first 6 months

Lightfoot et al. ScientififcWorldJournal 11:602-613 (2011)

- 10 yr DFS: 30%

von Rundstedt & Lerner Transl Androl Urol 4:244-253 (2015)

- Conventional intravesical chemotherapy has limited activity
  - e.g. doxorubicin, thiopeta, mitomycin

Kamat et al. Nature Rev Urol 12:225-235 (2015)

- Valrubicin the only FDA-approved drug for BCG **refractory CIS**
  - CR @ 6 month in 18%, 2yr disease free < 10%

Steinberg et al. J Urol 163:761-767 (2000)

Progression to MIBC

Review – Bladder Cancer

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

BJUI
BJU International

Progression to detrusor muscle invasion during urothelial carcinoma surveillance is associated with poor prognosis

19 trials incl. 3088 pts

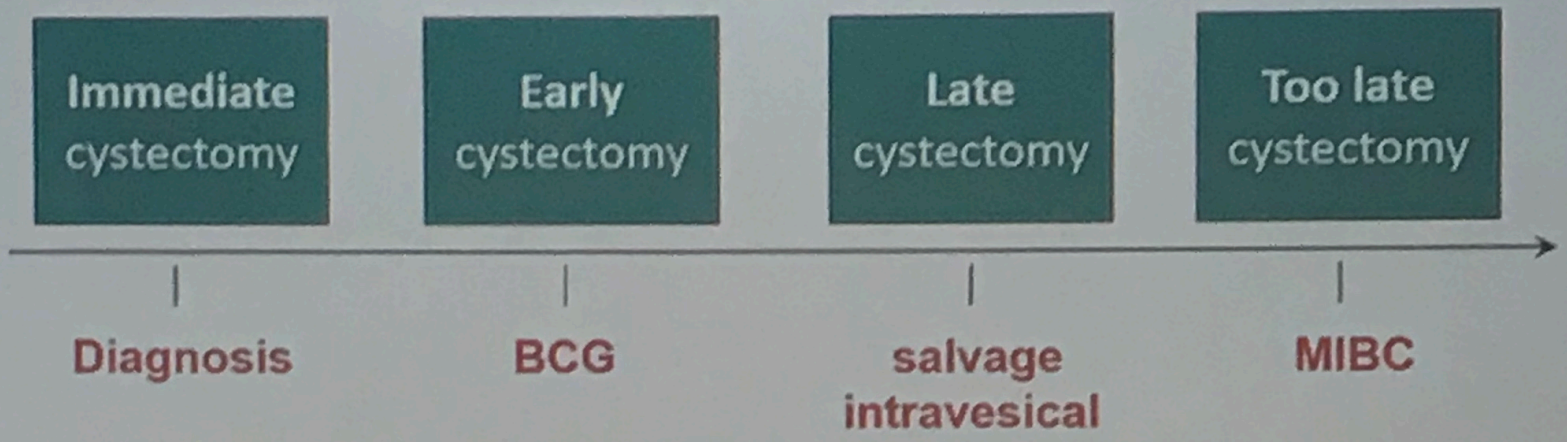
- 659 patients (21%) progressed to MIBC
- progression to MIBC and BCa-related death were relatively early events (<48 mo)
- **CSM 65% (428/659) of progressive patients**

Radical Cystectomy
5yr CSM

• before progression to MIBC (n=310)	14.6 %
• ***after progression to MIBC (n=190)***	***47.1 %***
• de novo MIBC (n=481)	37.6 %

van den Bosch et al. Eur Urol 60:493-500 (2011)

Likely of cure decreases with advancing disease stage



Conclusion

- **early HG recurrence** after BCG induction for **HR NMIBC (pT1 HG)**
- He should undergo **radical cystectomy**
  - or into clinical trial BCG/CPI; CPI; ...
- **Radical cystectomy should be offered** to patients with HR NMIBC
- when NOT removing the bladder would present
  a **loss of opportunity** to **CURE** the patient


Case description: important points
25 & 26 October 2019
Cité Internationale Universitaire
Paris, France
GLOBAL
CONGRESS
ON BLADDER
CANCER

Case description: important points

- PATIENT:
  - 65, without significant comorbidities
  - Asymptomatic except for haematuria
  - He would like to keep his bladder

Case description: important points

- PATIENT:
  - 65, without significant comorbidities
  - Asymptomatic except for haematuria
  - He would like to keep his bladder
- TUMOUR (at diagnosis):
  - Urothelial
  - primary
  - Single
  - pT1 HG without (diffuse?) CIS
  - Re-TURBT: No evidence of disease
  - Recurrence after induction BCG: TA HG

	BCG failure definition	Management of BCG failure
EAU	• Progression to MIBC • **high grade NMIBC at 3 months** • CIS at both 3 and 6 months • high grade tumor during therapy • Any high grade tumor after initial response and after completing maintenance	• **RC : preferred option** • ***treatments other than this should be considered oncologically inferior (LE 3)***
CUA	• **presence of high grade NMIBC at 6 months from TURBT (or at 3 months if the initial tumor was high-grade T1)** • any worsening of the disease while on therapy	• **RC is recommended (GR B)**
AUA	• **index patient #5 (high grade Ta/T1/Tis after prior intravesical therapy)**	• **RC : preferred option** • ***further intravesical therapy may be considered.***
NCCN	• high-grade T1 disease after induction BCG	• **RC is recommended** • ***non-surgical candidates can consider other options***
NICE	• fail induction course BCG	• **RC : preferred option** • ***patient unsuitable for RC: further intravesical therapy may be considered***

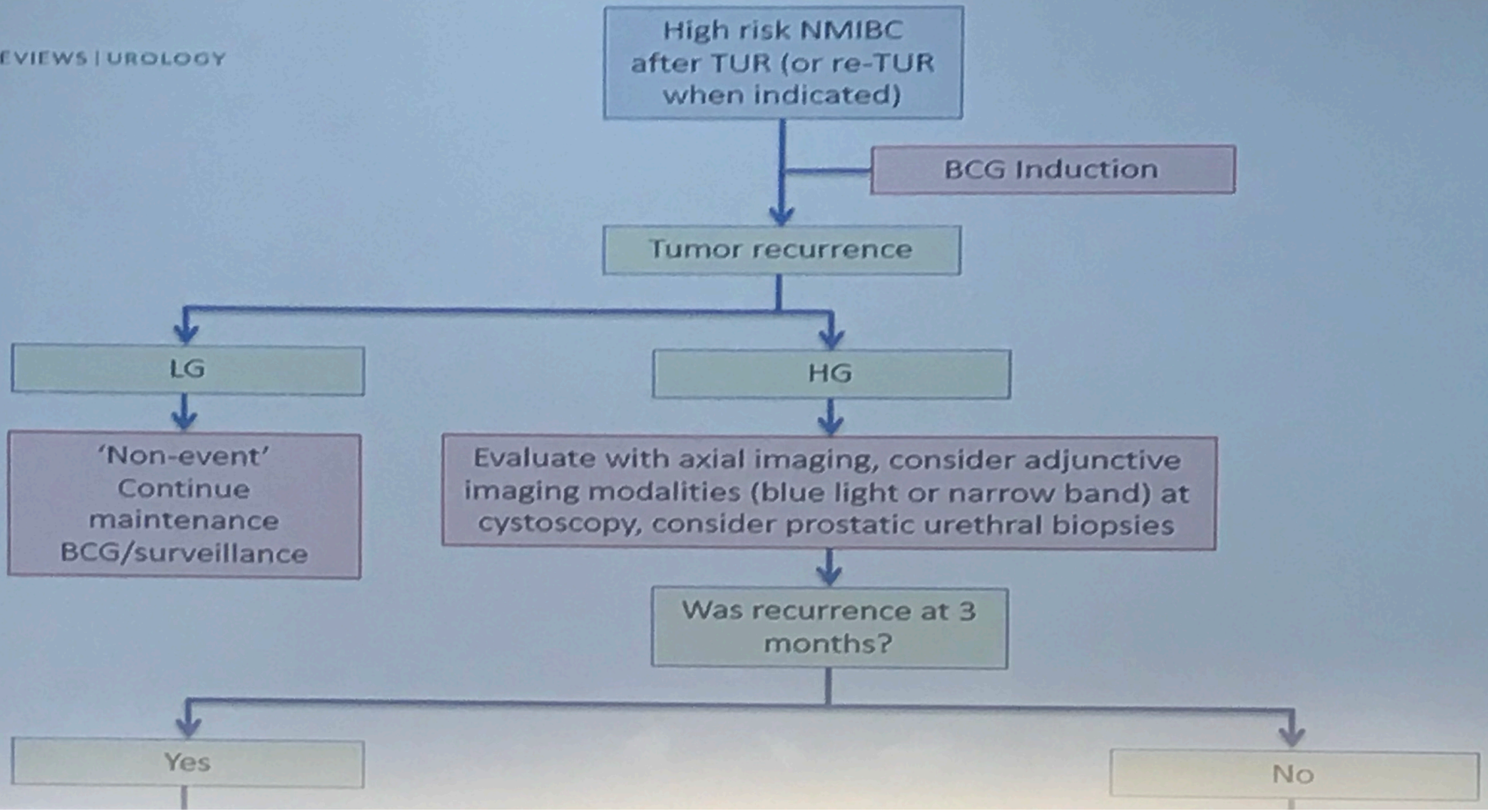
Nat Rev Urol. 2017 Apr;14(4):244-255

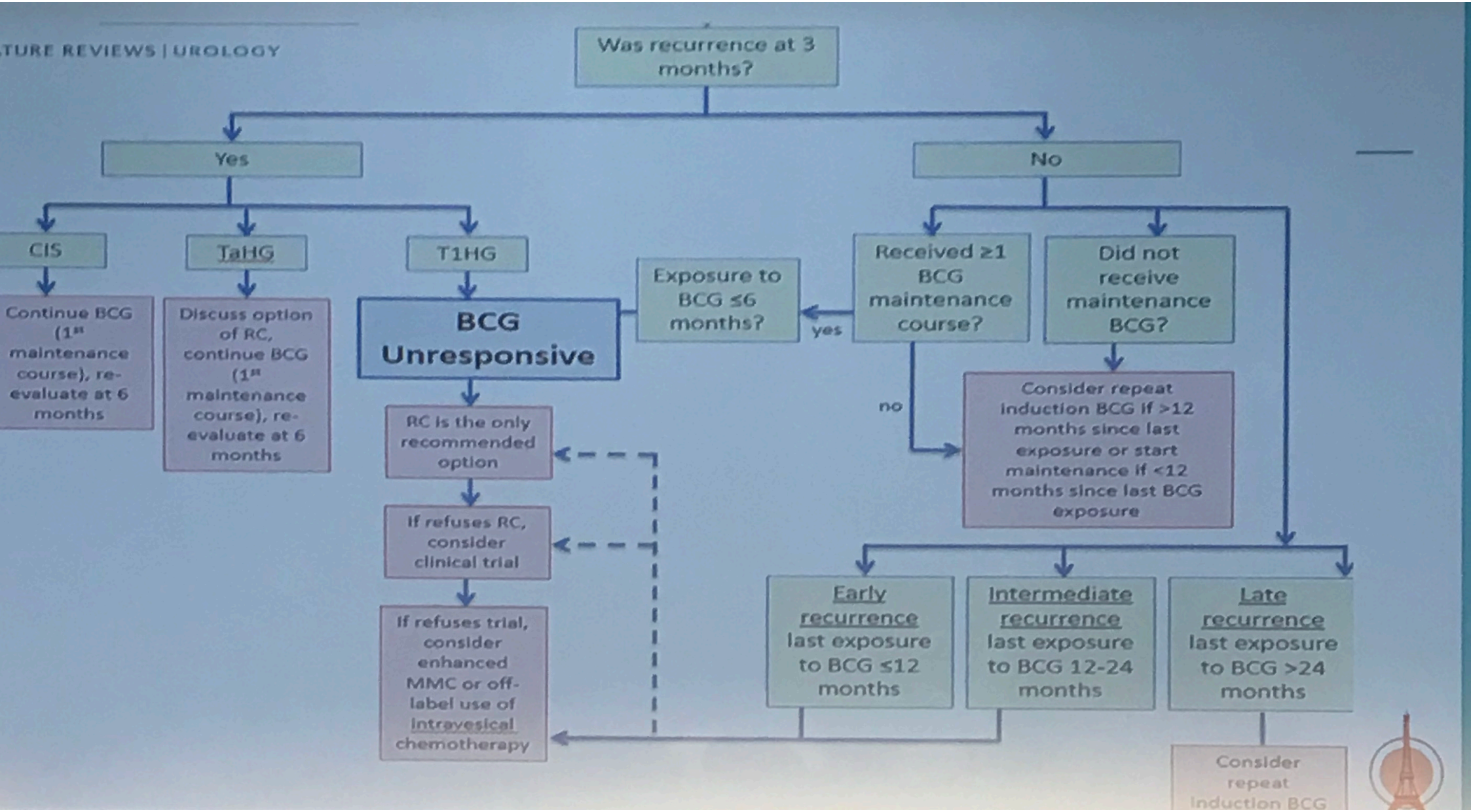
BCG Unresponsive Non-muscle Invasive Bladder Cancer: Definition, Treatment Options and Management Recommendations from the IBCG

Ashish Kamat[1], Marc Colombel[2], Debasish Sundi[1], Donald Lamm[3], Andreas Boehle[4], Maurizio Brausi[5], Roger Buckley[6], Raj Persad[7], Joan Palou[8], Mark Soloway[9], J. Alfred Witjes[10]

INTERNATIONAL BLADDER CANCER GROUP

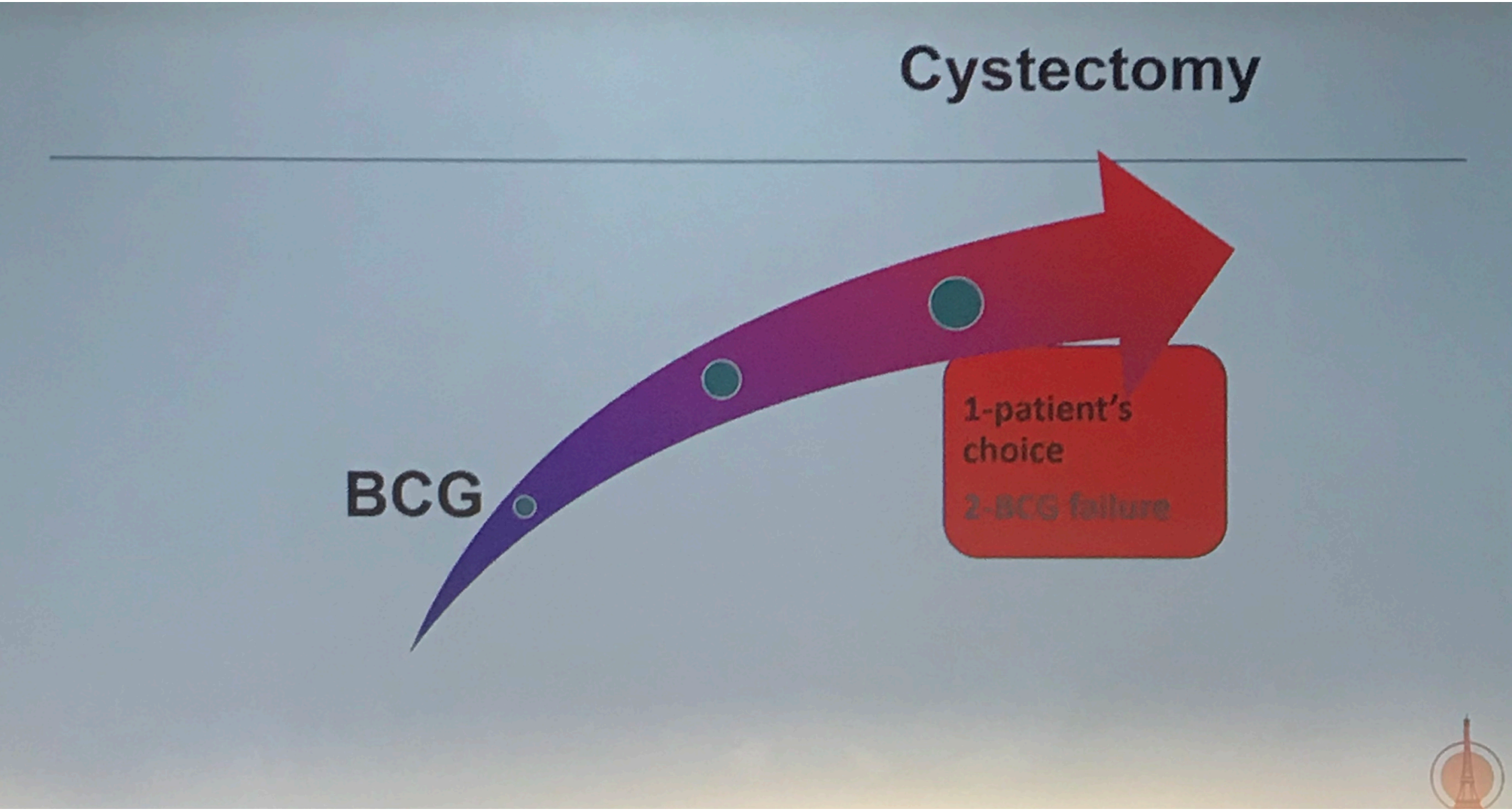
NATURE REVIEWS | UROLOGY

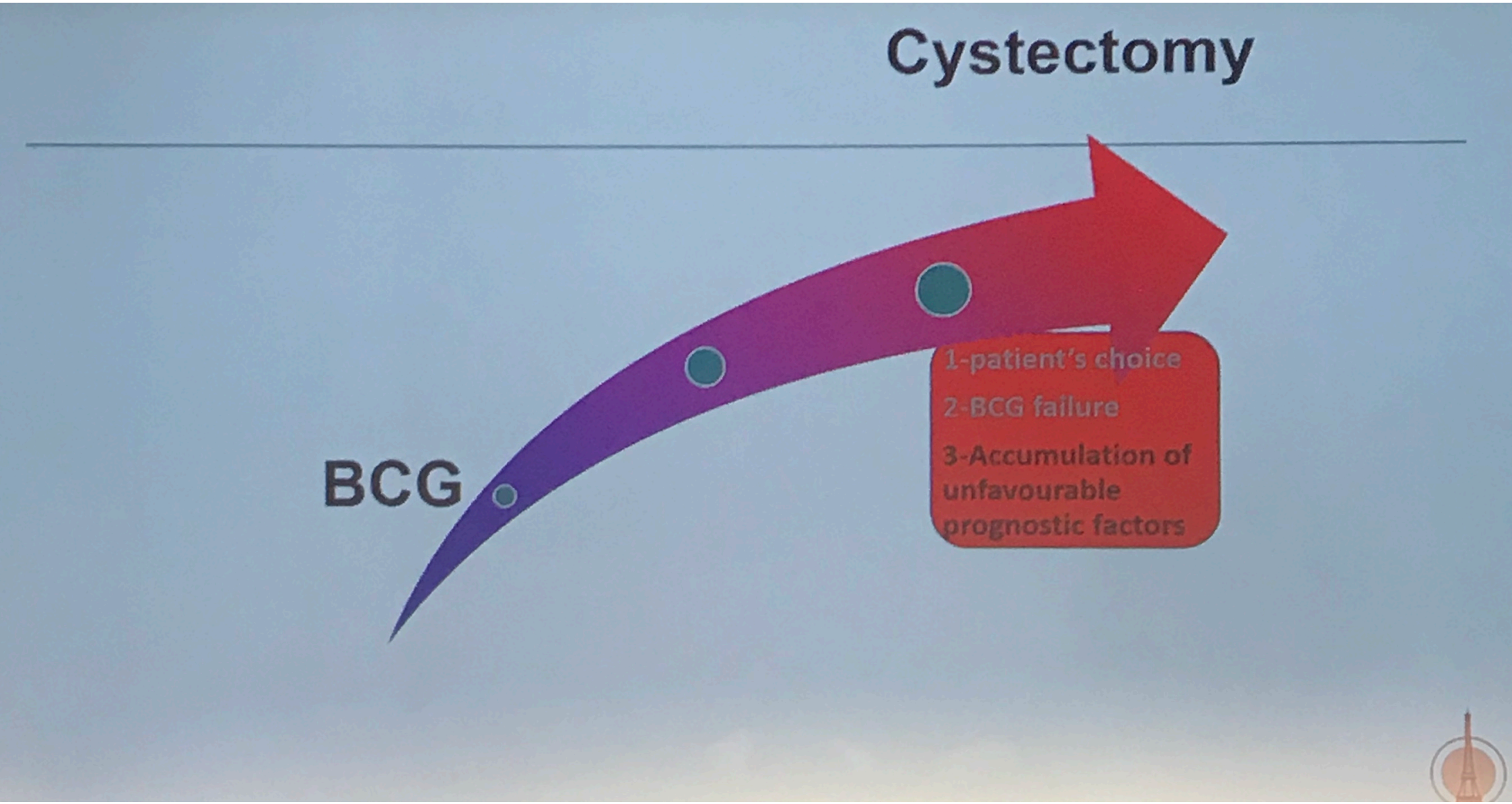



Was recurrence at 3 months?
Yes
No
CIS
TaHG
T1HG
Continue BCG (1st maintenance course), re-evaluate at 6 months
Discuss option of RC, continue BCG (1st maintenance course), re-evaluate at 6 months
BCG Unresponsive
Exposure to BCG ≤6 months?
yes
Received ≥1 BCG maintenance course?
Did not receive maintenance BCG?
no
Consider repeat induction BCG if >12 months since last exposure or start maintenance if <12 months since last BCG exposure
RC is the only recommended option
If refuses RC, consider clinical trial
If refuses trial, consider enhanced MMC or off-label use of intravesical chemotherapy
Early recurrence last exposure to BCG ≤12 months
Intermediate recurrence last exposure to BCG 12-24 months
Late recurrence last exposure to BCG >24 months
Consider repeat induction BCG

T1HG: a heterogeneous disease

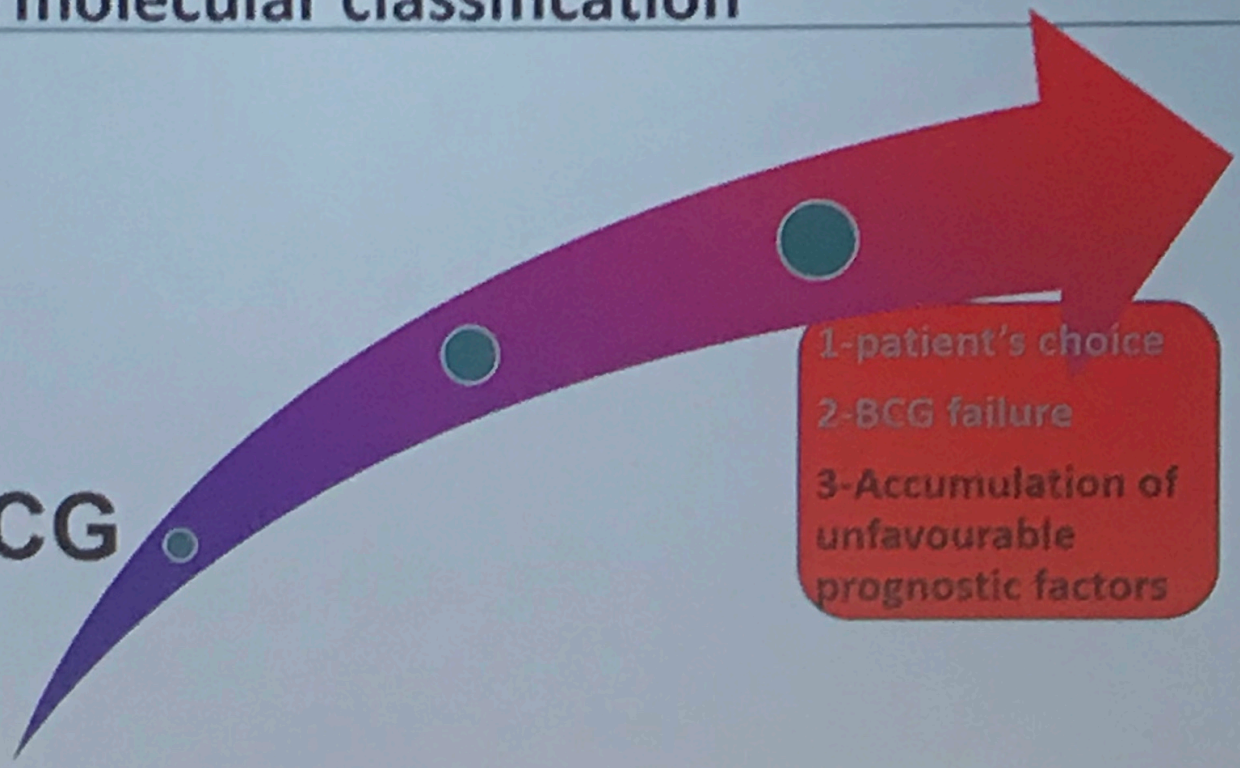
Management strategy


Cystectomy
BCG
1-patient's choice
2-BCG failure


Cystectomy
BCG
1-patient's choice
2-BCG failure
3-Accumulation of unfavourable prognostic factors

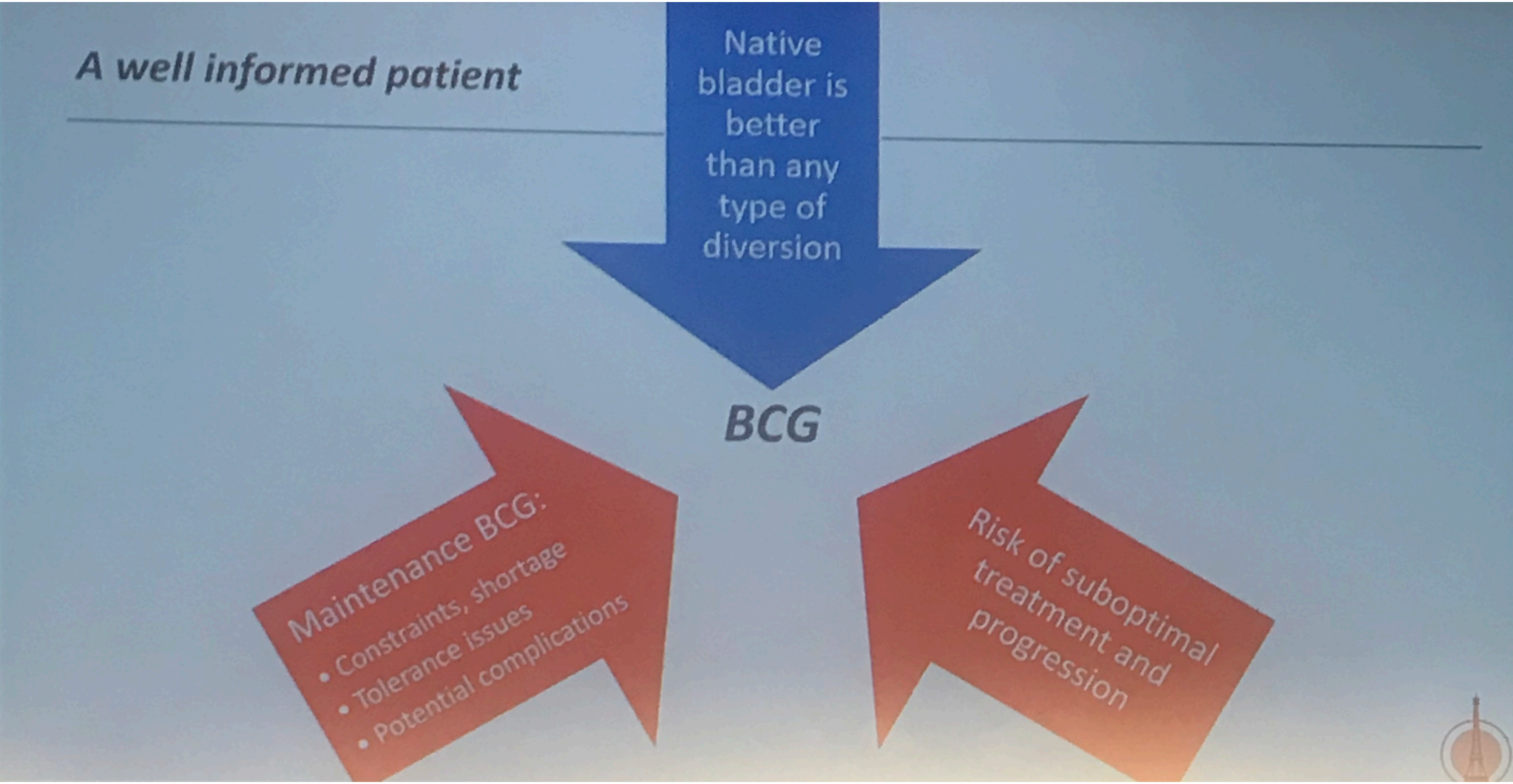
Cystectomy

Pending a reliable molecular classification



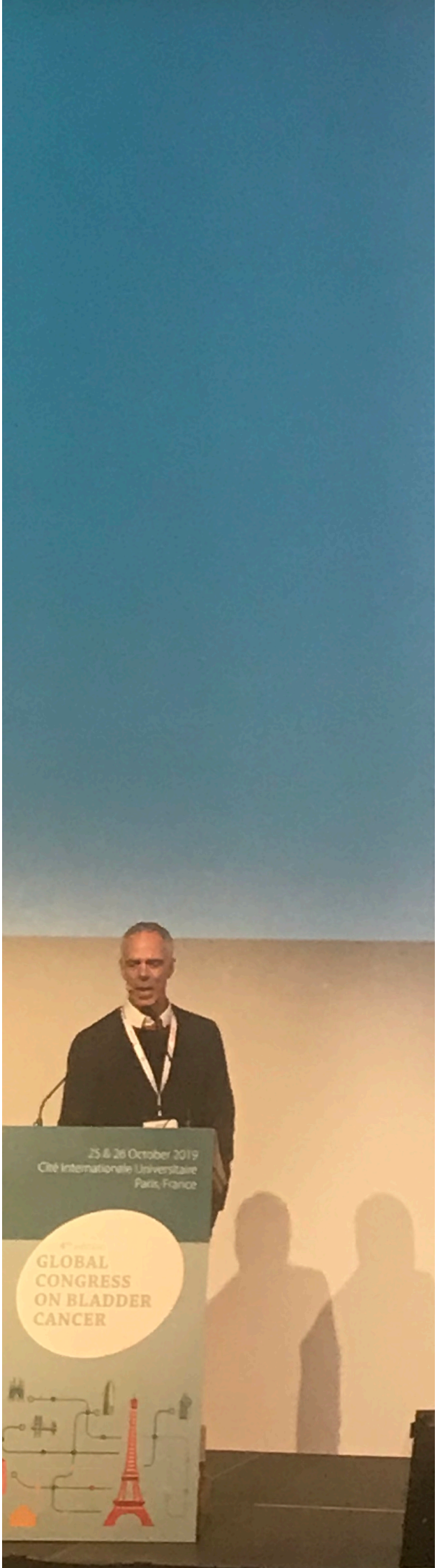
Favourable prognostic factors- Tumour :

- First
- Single
- <3cm
- T1a (no invasion beyond the muscularis mucosa)
- T0 at repeat TURB
- No CIS
- No variant (eg micropapillary)
- No LVI


A well informed patient
Native bladder is better than any type of diversion
BCG
Maintenance BCG:
• Constraints, shortage
• Tolerance issues
• Potential complications
Risk of suboptimal treatment and progression

Trimodality therapy for BCG-unresponsive NMIBC: Give the patient a chance

Anthony Zietman MD
Shipley Professor of Radiation Oncology
Harvard Medical School
Massachusetts General Hospital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CANCER

Patients don't want to have their bladders removed

Selective Bladder Preservation against Radical Excision (SPARE)

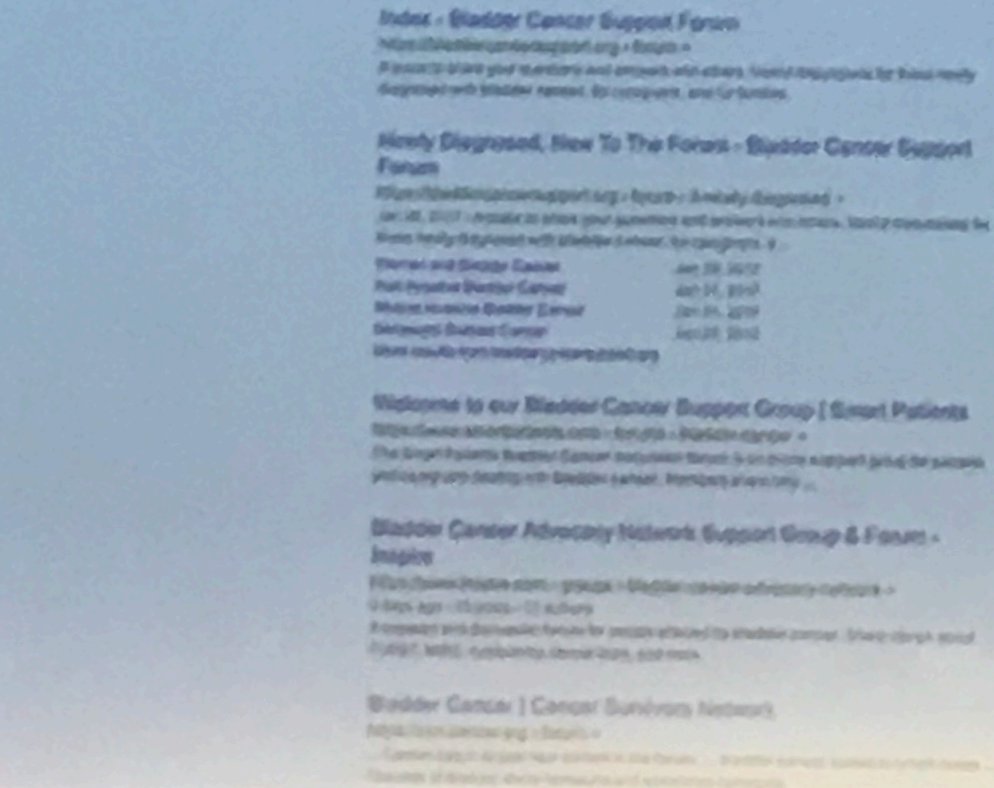
Failed to accrue target 800 patients because patients either wouldn't accept randomization or "jumped ship" from RC to TMT

Huddart BJC 2017

Patients work to avoid having their bladders removed

100s of bladder cancer patient info and support forums

- most discuss bladder preservation

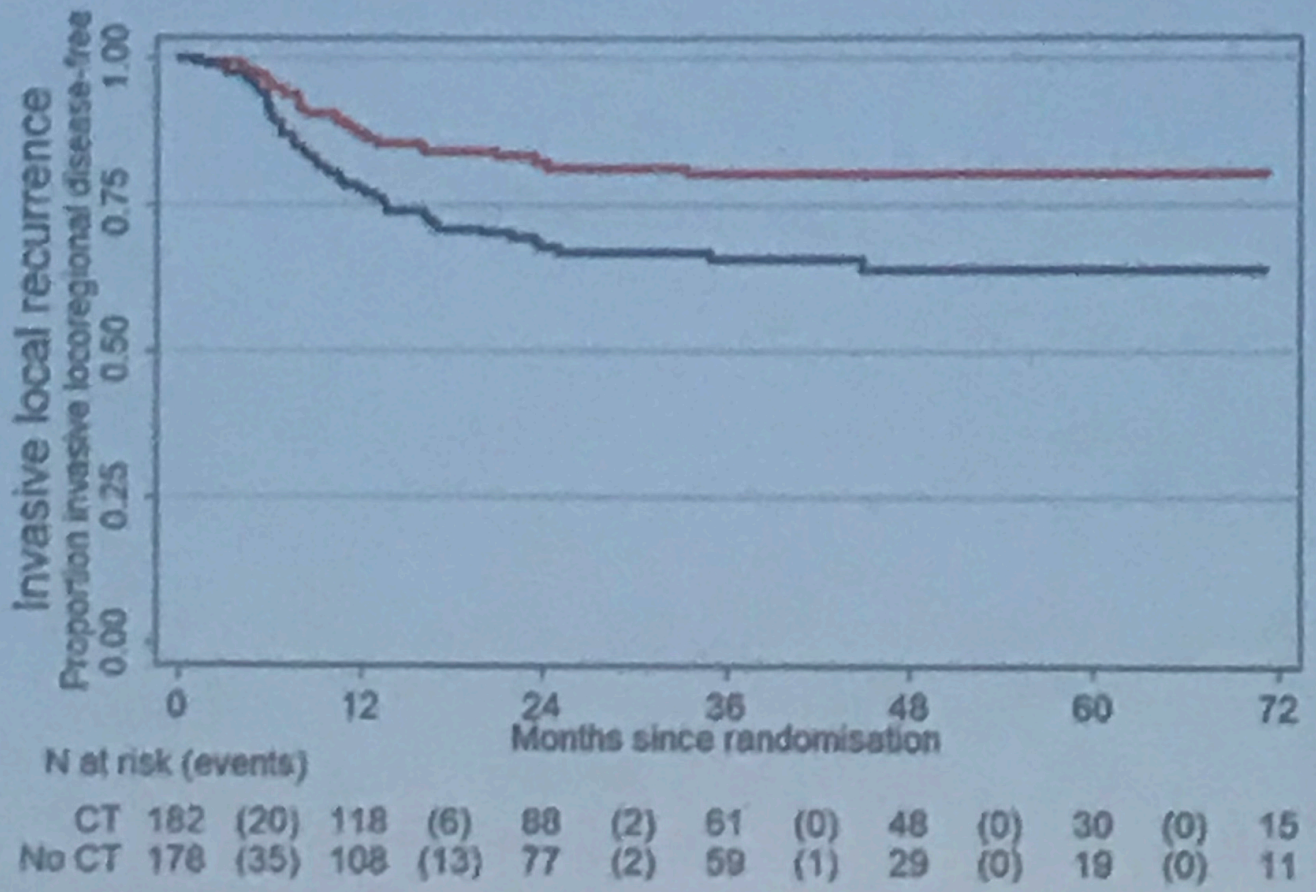


The cystectomy is a tough gold standard

>90% local control but……..

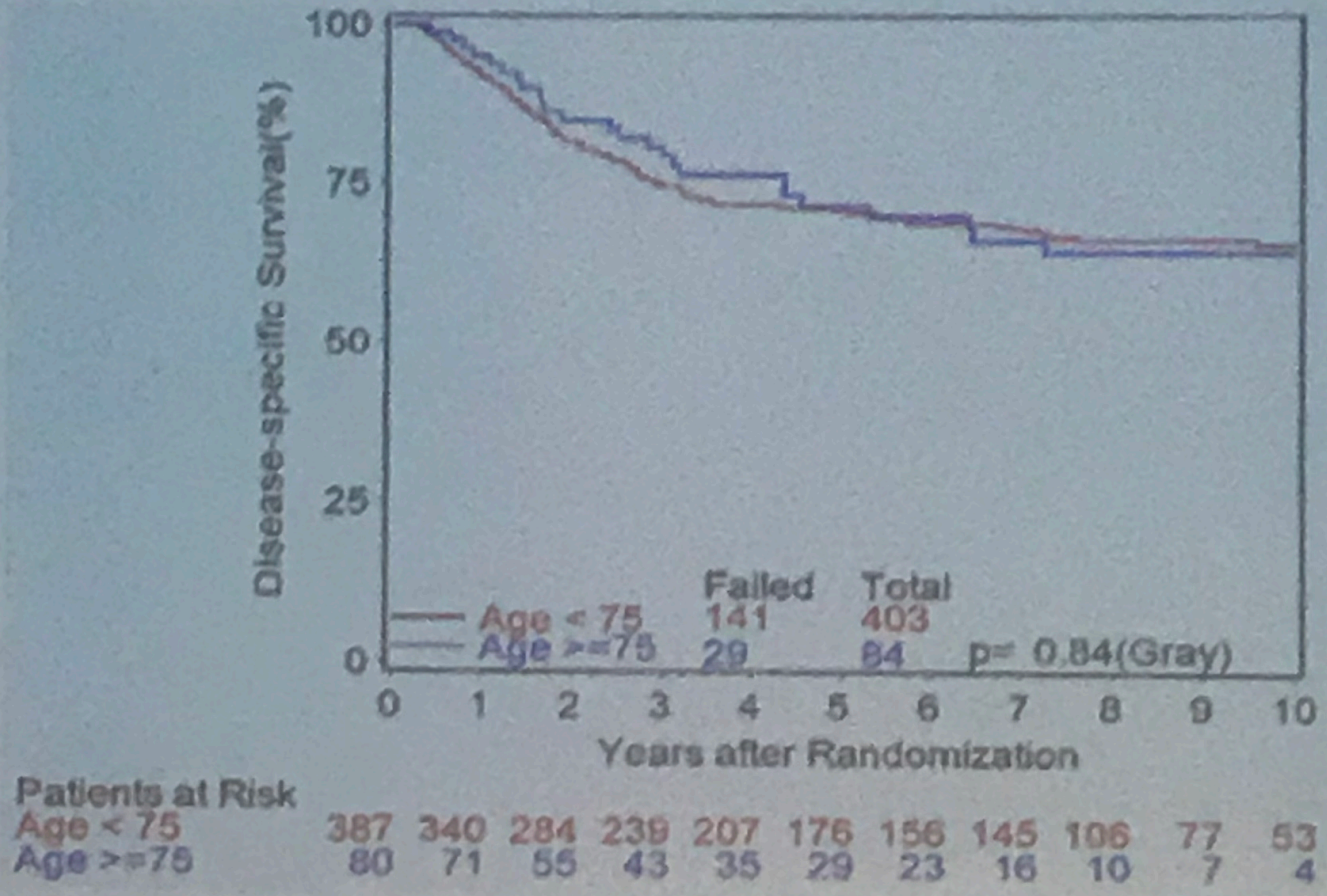
- Morbidity and mortality
- Overtreatment – those who could be controlled other ways
- Undertreatment – those with occult nodes

Trimodality therapy has a strong track record in MIBC



James et al. N Engl J Med 366: 1477-88, 2012

Both younger and older patients fare well long-term



Mak et al. Pooled analysis of RTOG protocols. JCO:2014

Trimodality therapy has good QOL outcomes

221 patients, T2-4NX-0M0 bladder cancer, median FU 6 years

Urodynamic study, QOL questionnaire

- 78% have compliant bladders with normal capacity and flow parameters
- 85% have no urgency or occasional urgency
- 25% have occasional to moderate bowel control symptoms
- 50% of men have normal erectile function

Zietman, Talcott, Krane et al J Urol 2003

Comparing long-term QOL in those treated by CMT and RC

- 226 eligible patients
  - 173 completed the questionnaire (response rate: 77%)
  - 109 patients (63%) received RC
    - 89 ileal conduit and 18 neobladder diversions
  - 64 patients (37%) received CMT
    - 6 patients (9%) required salvage cystectomy

- Median time from diagnosis to questionnaire was 6 years for RC vs. 9 years for CMT (p=0.009)

Mak, K. et al IJROBP 2017

Study conclusions

- CMT associated with modestly higher general HRQOL and bowel function scores vs. RC
  - CMT markedly better sexual scores vs. RC

- CMT associated with better perception of informed decision-making, and less concern about body image/changes, life interferences, and negative impact of cancer

Mak, K. et al IJROBP 2017

High-grade NMIBC is often under-staged

Dutta et al J. Urol 2001

30% prove to be at least T2 in the cystectomy specimen

Thus……

T1 disease is often already MIBC
and when not, can be considered a *"baby" T2*

High-grade NMIBC is often under-staged

Dutta et al J. Urol 2001

30% prove to be at least T2 in the cystectomy specimen

Thus.....

T1 disease is often already MIBC
and when not, can be considered a *"baby" T2*

Evidence for radiation-based techniques in high-risk NMIBC

Weiss 2006	141	TURBT, RT, cisplatin	DSS similar to RC series PD similar to BCG
Harland 2007	210	RCT Obs vs RT BCG vs RT	RT alone added nothing
NRG 2019 (unpublished)	37	RT + either cisplatin or 5FU/MMC	Low rates of cystectomy

Chemo-radiation takes little time

No neo-adjuvant or adjuvant chemotherapy required

4 - 6.5 weeks maximum

In other cancers we retrofit data to earlier disease

Cancer of H&N T2-4 – chemo-radiation is SOC

also used in T1 and pTis

Cancer of the Breast – tri-modality therapy is the SOC

also used in DCIS

MIBC– tri-modality therapy is a SOC

Should also be considered in high-risk NMIBC

Radiation is a potent immunotherapy adjuvant

Melanoma	RT + nivo/ipi
Lung cancer	RT + pembro

?Bladder cancer

- BCG is an early form of immunotherapy
- Trials of radiation with atezolizumab (anti-PDL-1)

Chemo-radiation is approved by the NCCN, EAU, AUA, and UK treatment guidelines for MIBC

Time it was considered in HG-NMIBC:

- For those who are doomed to fail with intravesical agents
- For those unfit or too elderly for cystectomy
- To select those who truly need cystectomy

There is nothing special about high-risk NMIBC

It is a nasty MIBC "in disguise" and should be treated accordingly

There is no unique molecular or biological reason that it will be less sensitive to chemo and RT than T2

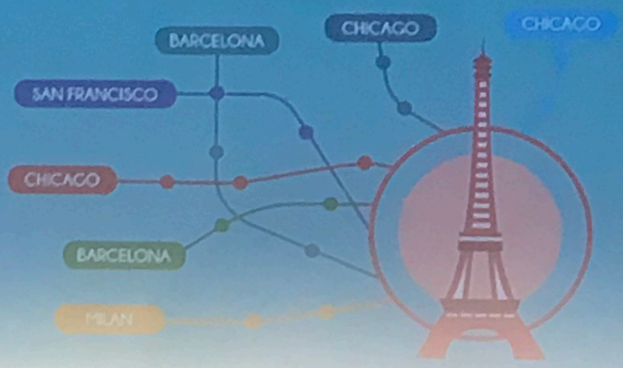
Give the patient one last chance

GLOBAL CONGRESS ON BLADDER CANCER

Intravesical therapy (ROUND 2)

Jacques Irani, Urology

Paris, France



Do not decide for a T1HG management without having every available information

VOLUME 33 · NUMBER 6 · FEBRUARY 20 2015

JOURNAL OF CLINICAL ONCOLOGY

REVIEW ARTICLE

Improving Selection Criteria for Early Cystectomy in High-Grade T1 Bladder Cancer: A Meta-Analysis of 15,215 Patients

William Martin-Doyle, Jeffrey J. Leow, Anna Orsola, Steven L. Chang, and Joaquim Bellmunt

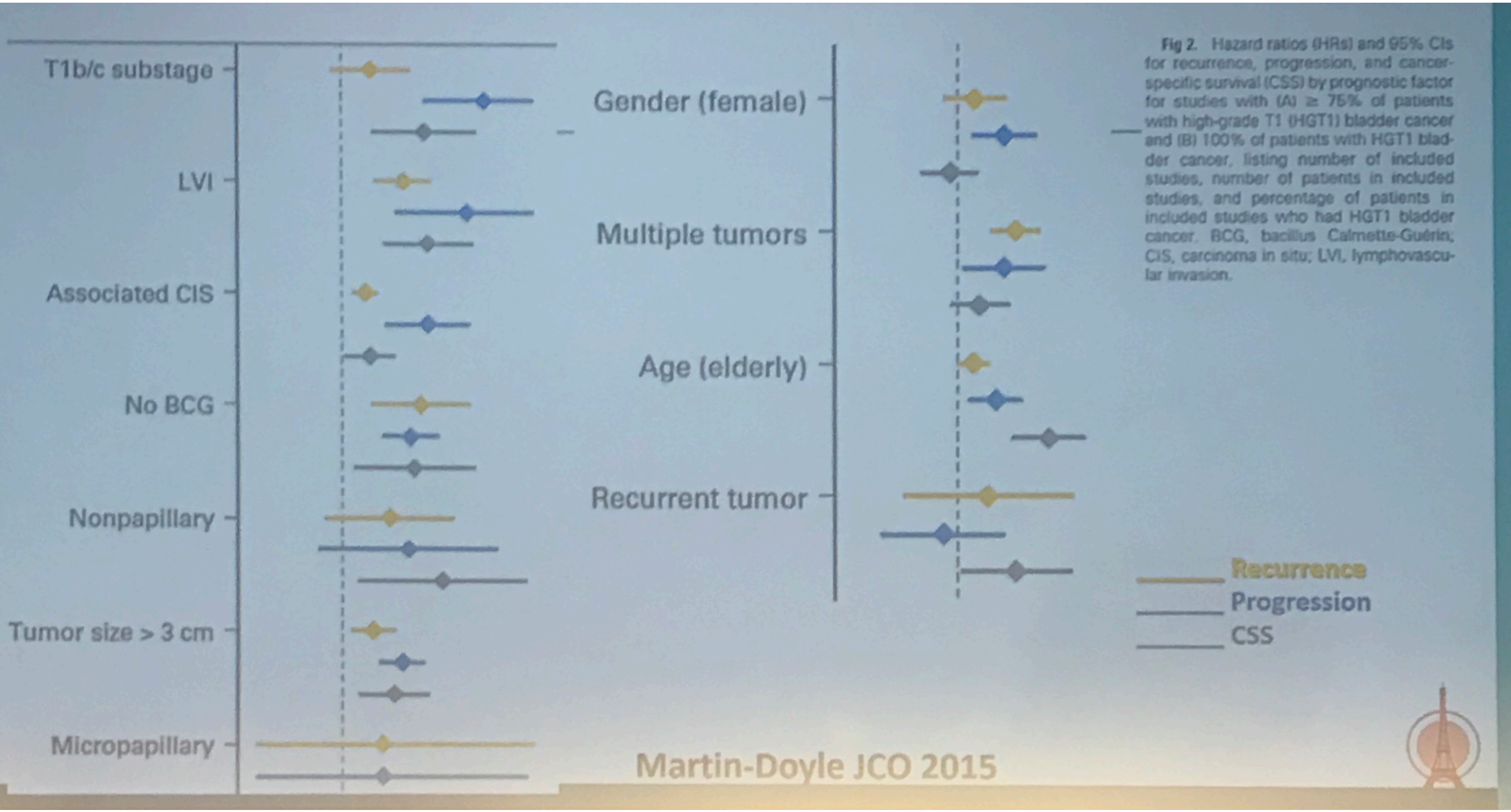
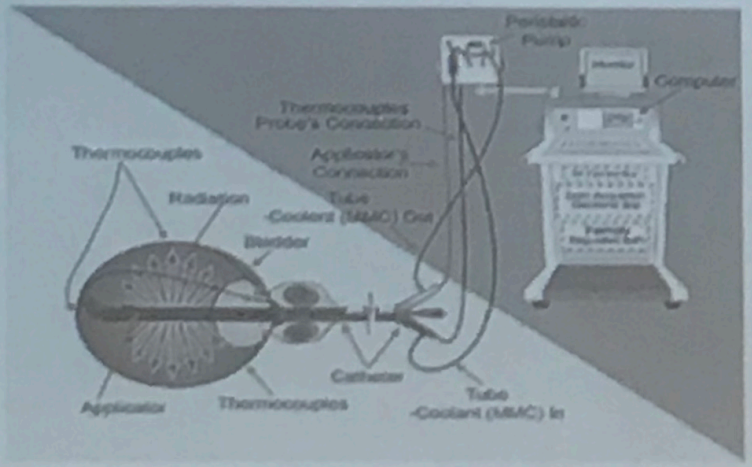


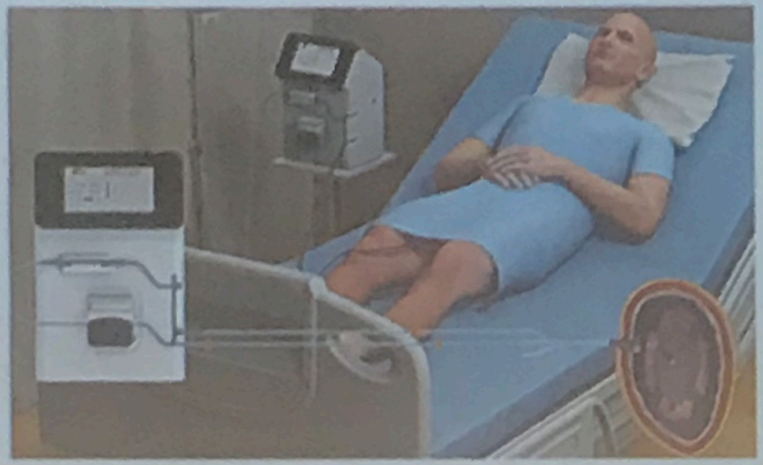
Fig 2. Hazard ratios (HRs) and 95% CIs for recurrence, progression, and cancer-specific survival (CSS) by prognostic factor for studies with (A) ≥ 75% of patients with high-grade T1 (HGT1) bladder cancer and (B) 100% of patients with HGT1 bladder cancer, listing number of included studies, number of patients in included studies, and percentage of patients in included studies who had HGT1 bladder cancer. BCG, bacillus Calmette-Guérin; CIS, carcinoma in situ; LVI, lymphovascular invasion.

Stay tuned!

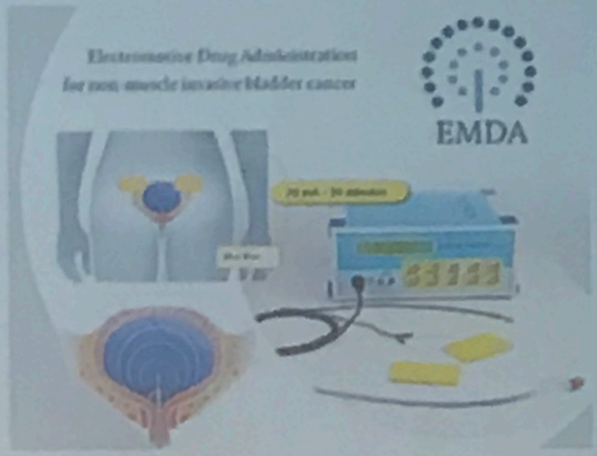
RITE



HIVEC



EMDA



Stay tuned!

Agent	Phase 2
• **Vicinium** EpCAM-specific antibody fragment fused to a potent pseudomonas toxin)	✓
• **CG0070** oncolytic adenovirus	✓
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Trimodality therapy for high-risk T1 cancer:

Anthony Zietman MD
Shipley Professor of Radiation Oncology
Harvard Medical School
Massachusetts General Hospital

There is nothing special about a high-risk T1 NMIBC

It is a nasty, proto-MIBC and should be treated accordingly

There is no unique molecular or biological reason that it will be any less sensitive to chemo and RT than T2

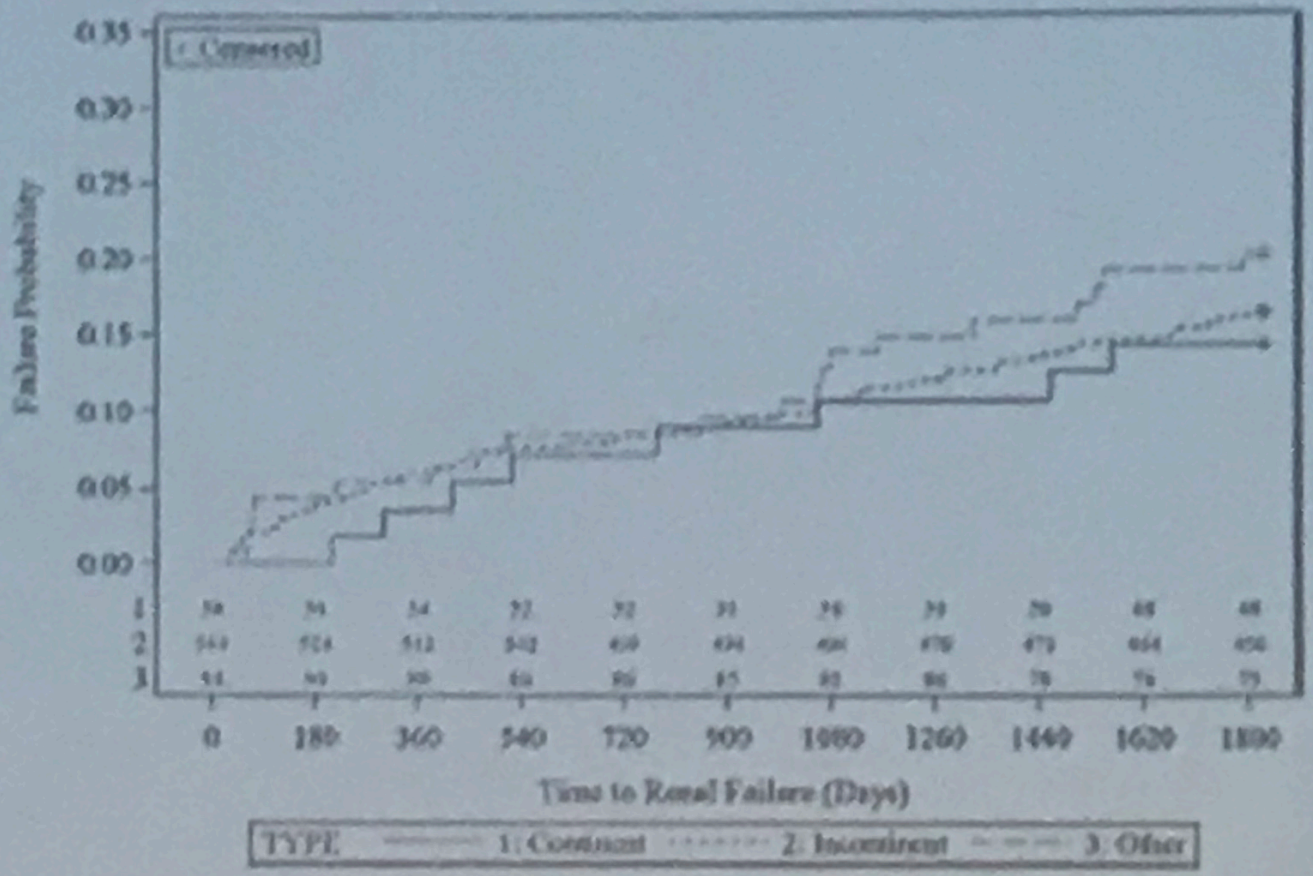
Remember the short and long-term consequences of the cystectomy

Donat et al 2009

64%	More than 1 grade ≥ 2 complication
13%	Grade 3-5
26%	Readmissions
2.7%	90 day mortality

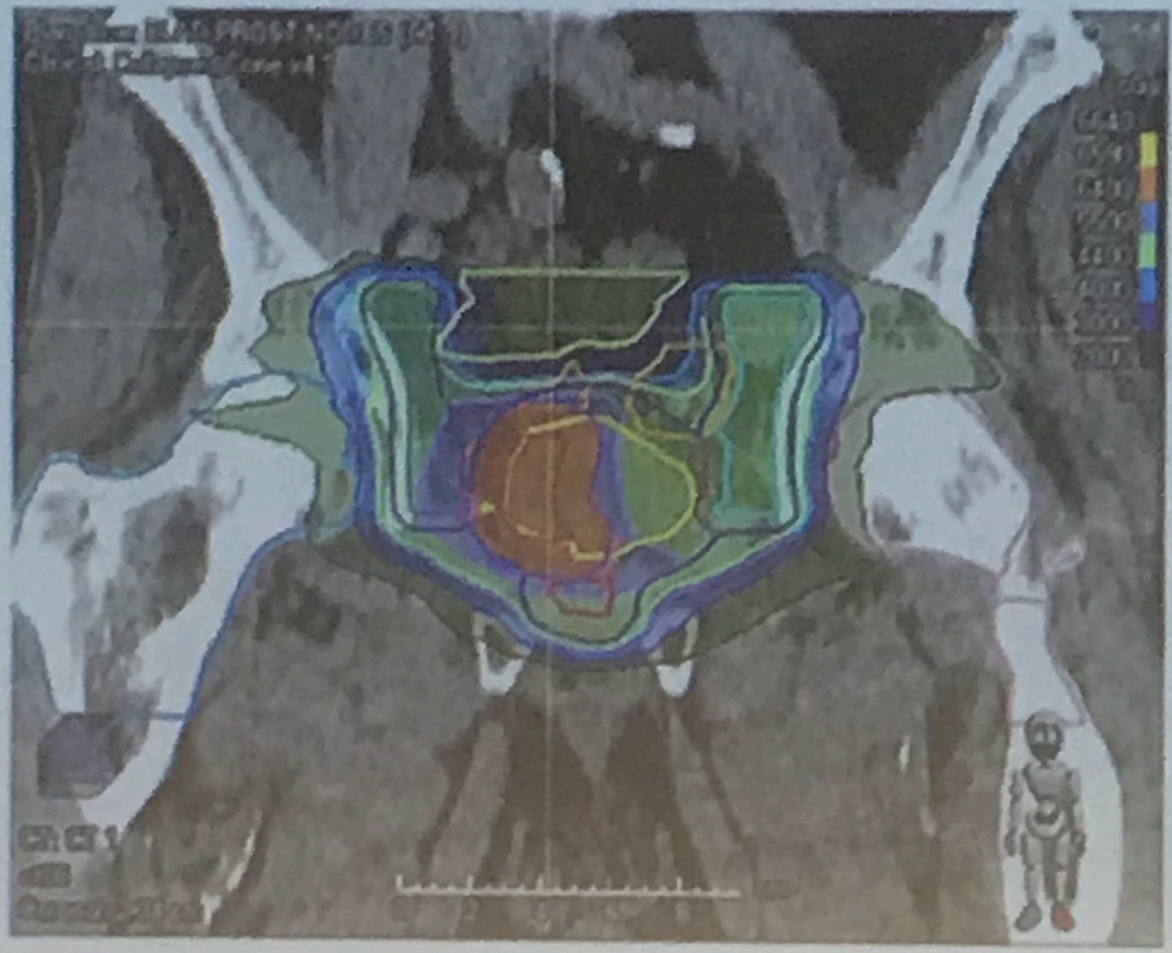
Eur Urol 55: 177, 2009

Remember the short and long-term consequences of the cystectomy

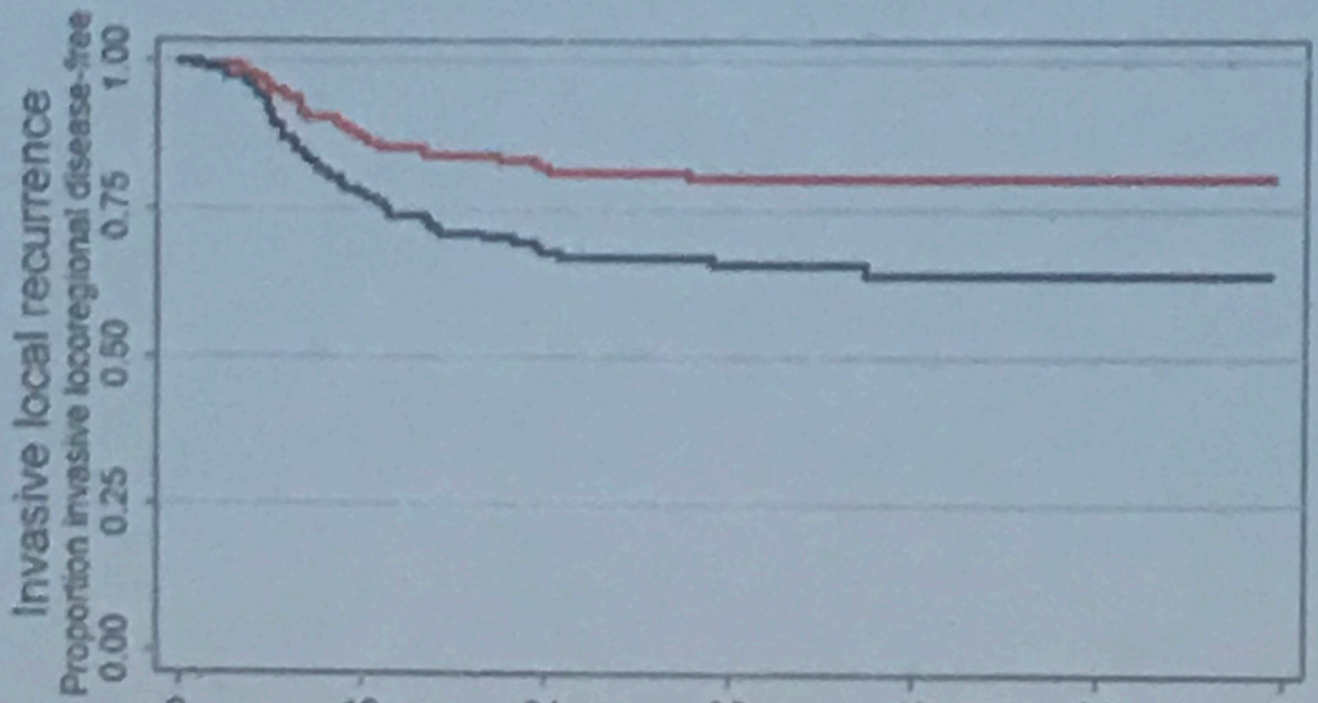


The risk of renal failure or significant impairment 5 years after urinary diversion approaches 16%

Remember that radiation has greater reach than any intravesical therapy



Remember the good outcomes for TMT in MIBC



N at risk (events)

CT	182	(20)	118	(6)	88	(2)	61	(0)	48	(0)	30	(0)	15
No CT	178	(35)	108	(13)	77	(2)	59	(1)	29	(0)	19	(0)	11

James et al. N Engl J Med 366: 1477-88, 2012

Use TMT to select those who truly need a cystectomy

From TURBT through chemo-RT is, at most, 7 weeks

- The majority will not need cystectomy
- Those that do will have it with little delay and knowing that they really need it

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The best bladder you will ever have is the one you were born with