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What is success for CIS?

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RESEARCH TREATMENT
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Disclosures

- **Consultant:** AbbVie, Astellas, AstraZeneca, BMS, Bayer, EMD Serono, Ferring, Fergene, Janssen, MDxHealth, Merck, Prokarium, Protara, QED, Roche, Sanofi, STIMIT, Therelase, UroGen, Verity
- **Speaker:** Pfizer, BioSyent, TerSera, Sanofi, Bayer
- **Clinical Trial:** Genentech, AstraZeneca
- **Patent:** Decipher

Two existential questions in CIS trials

Is CIS always a diffuse disease?

(i.e. how many CRs are due to complete resection)

How good are we at detecting CIS?

(i.e. how many CRs are a failure to detect?)

Is CIS completely resectable?

- Bladder cancer arises in background of diffuse field effect
  - Does this impact papillary NMIBC and CIS differently?
- CIS is flat and therefore more difficult to visualize than papillary NMIBC
- We know we miss 40% of CIS lesions on WL compared to BL[1]
  - CIS detected by BL only in 27% of patients with NMIBC
- CIS is typically visualized on BL as well-defined and resectable lesion(s)
- Data is sparse, but some bladder CIS is likely resectable
  - Studies do not report recurrence rates for CIS specifically after BL vs WL
- **Some CRs in trials likely due to TURBT and not drug effect (similar to Ta/T1)**

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[1] Burger et al, Eur Urol 2013

Could blue light make CIS resectable?

- pooled data from 3 phase III studies comparing BL vs WL for detection of CIS
- 551 patients: 174 (32%) had ≥1 CIS lesion detected by BL, WL, or random biopsy
- CIS detection rate 87% for BL and 75% for WL (p=0.006) (n=13 by random biopsy only)
- BL was less likely to detect CIS in patients previously treated with chemotherapy or BCG (P=0.01 and 0.03, respectively) after adjusting for age

Number of CIS detected with any method in 174 patients

No. of CIS lesions	*n* (%)
1	77 (44.3)
2	40 (23.0)
3	18 (10.3)
4	21 (12.1)

Mean: 1.9 lesions per patient

CIS was unifocal in 44% and multifocal in 56%

No studies have investigated outcomes after BL vs WL for CIS patients specifically

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Lerner et al, Urol Oncol 2012

Table 2 – Natural history of carcinoma in situ treated only with biopsy/fulguration

Study	Subjects, *n*	CIS type	Management	Progression-free survival, mo (range)	Progression rate (%)
Utz et al [30]	62	NA	Fulguration with or without TUR Segmental resection	NA (60–144)	37 (60)
Wolf et al [31]	31 26	Primary Secondary	Cold biopsy with or without TUR	4 (74–129)	16 (52) at 59-mo mean
Herr et al [32]	24	NA	TUR	18 (12–24)	12 (50)
Cookson et al [33]	21	Including Ta/T1	TUR only	6 (3–181)	17 (81)
Jacobsen et al [34]	19	Primary	Surveillance	23 (7–56)	10 (53) at 46-mo mean
Fukui et al [35]		(Ta, T1)			
Melamed et al [36]	17	NA	Fulguration with or without TUR	27 (1–63)	10 (59) at 25-mo mean
Farrow et al [37]	17	NA	Fulguration with or without TUR	40 (7–84)	7 (41)
Althausen et al [38]	12	NA	Fulguration with or without TUR Segmental resection	23 (1–72)	10 (83) at 18-mo mean
Prout et al [39]	12	Primary	TUR	34 (3–60)	9 (75) at 32-mo median
Riddle et al [40]	6	NA	Not specified	49 (6–84)	0

CIS = carcinoma in situ; NA = not available; TUR = transurethral resection.

Historically: high progression rate with TUR alone

Casey et al, Eur Urol 2015

Does the CIS +/- Ta/T1 mix matter?

Is pure CIS more likely to be a diffuse disease that is:

- not amenable to complete resection?
- more likely to be detectable on subsequent surveillance?

Concomitant CIS may be focal incidental finding adjacent to Ta/T1

	Pure CIS	CIS + Ta/T1	CIS + T1
S1605	58%	42%	22%
Nado	76%	24%	5%
KN57	63%	37%	12%
QUILT	69%	31%	9%

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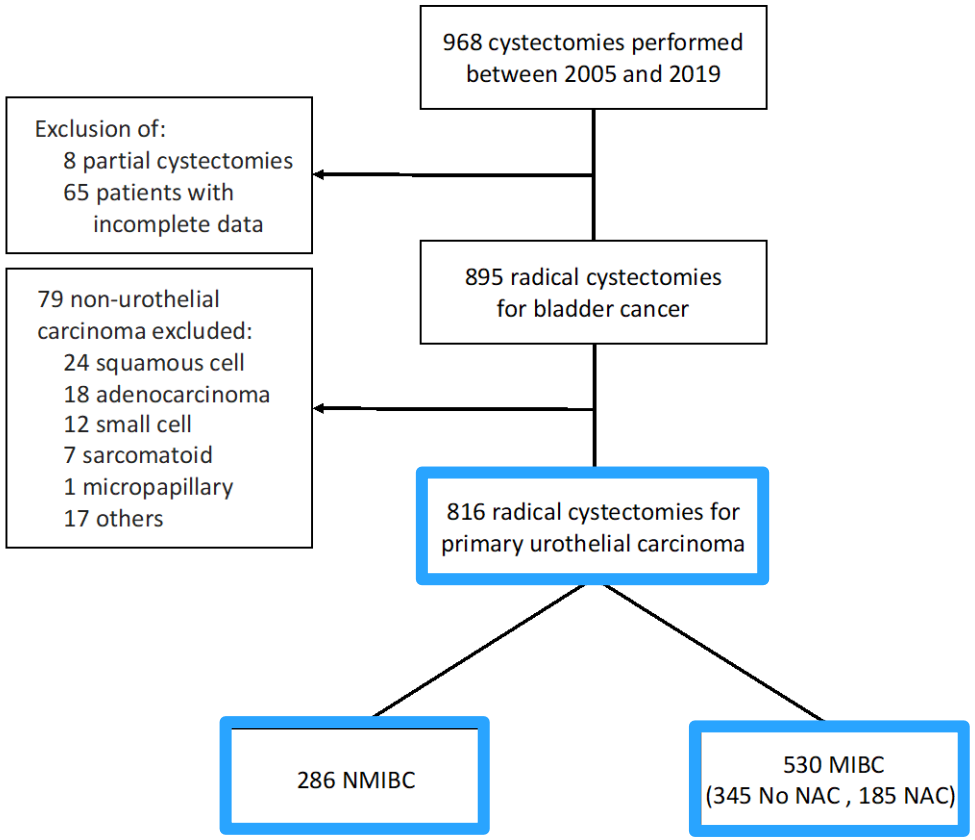
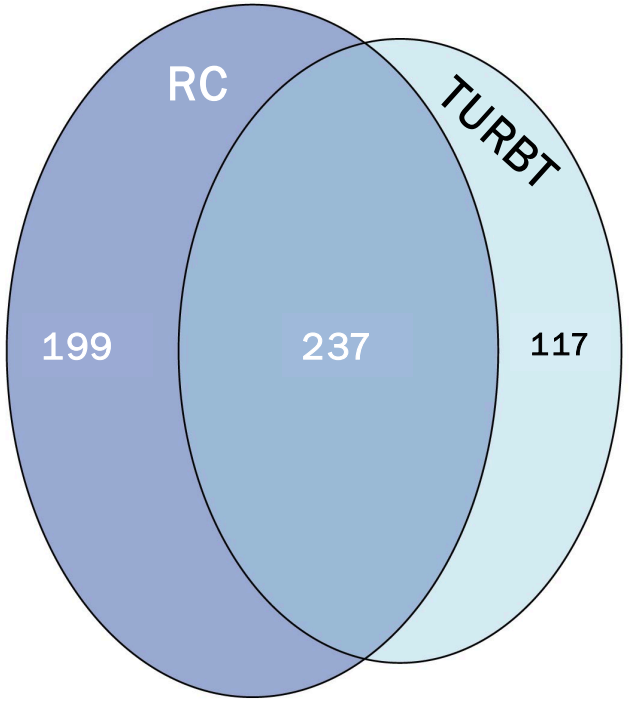
Poor concordance of CIS detection between TURBT and RC highlights limitations in detection





CIS was detected in 553 (68%) patients

21% of patients with CIS on TURBT had no CIS on RC
- completely resected on TUR or missed on RC pathology?

36% of CIS at RC was not detected by prior TURBT
- 20% if RC for NMIBC
- 47% if RC for MIBC

Roumiguié & Black, unpublished

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Ability to detect CIS

- Nadofaragene trial
  - 23 of 48 (48%) patients with Ta/T1 recurred
    - rate of CIS on TUR not reported
  - 5 of 11 (45%) patients in the Ta/T1 cohort who underwent cystectomy had CIS

- S1605
  - 31 of 55 (56%) patients with Ta/T1 recurred
    - 7 of 31 (23%) had CIS on TUR at time of recurrence

Boorjian et al, Lancet Oncol 2020
Black et al, ASCO 2021

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Other critical questions

Timing of CR

Criteria for CR: Cytology

Criteria for CR: Mandatory Biopsy

Consider impact of systemic vs local therapy

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At which timepoint should the CR rate for CIS be determined?

- For drug with immune mechanism: 6 months has been suggested as primary endpoint so that delayed responses (after 3 months) can also be captured.
  - Short-term risk of progression to MIBC is low in recent trials in patients with BCG-unresponsive NMIBC, so the risk to patient of waiting additional 3 months should be acceptable
- For drug without immune-based mechanism: should the primary endpoint be CR at 3 months?
- However, need uniform timepoint in trials that compare immunotherapies with non-immune-based therapies

Positive Cytology in Clinical Practice

- High specificity of positive cytology makes us assume patient has cancer and we just need to find it
  - Critical to assess upper tract and prostatic urethra
  - Blue light cysto especially important if no visible lesion in bladder
  - Repeat evaluation if cancer not detected
- "Suspicious" cytology typically leads to similar evaluation
  - But less specific (more false positives) and therefore should not be considered "positive" in definition of trial endpoints

Positive Cytology in Clinical Trial

- Positive cytology may come from upper tract or urethra
  - If local (intravesical) therapy only, should positive cytology NOT constitute recurrence?
  - If systemic therapy only, should positive cytology constitute recurrence?
- Cross-trial comparisons will be very challenging if the definitions of CR are different.

Why consider mandatory re-biopsy?

CIS can be invisible

Changes related to intravesical therapy make cysto/cytology difficult to interpret

Remove urologist bias in interpretation of indeterminate lesions

Mandatory Re-Biopsy

The 2018 FDA Guidance “recommends” random biopsy during trial for BCG-unresponsive CIS,

- inadequate evidence to **require** random biopsies
- trials have therefore been inconsistent
- Several trials incorporate “for-cause” biopsies only (triggered by abnormal cystoscopy or cytology)

When to do mandatory re-biopsy?

Makes most sense at time of primary endpoint

Is mandatory re-biopsy required in randomized trial design?

Less important provided the treatment arms are blinded

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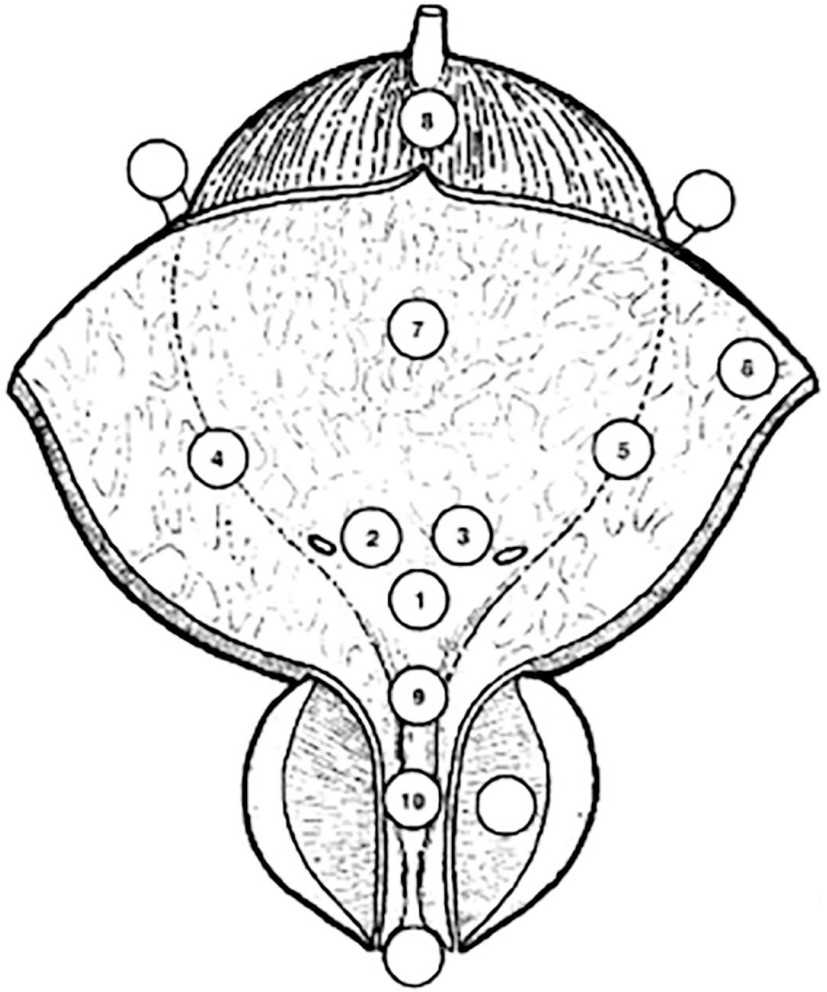
Important: mandate a methodology for biopsy

- ≥5 sites from different areas of bladder wall (“random biopsies”)
- Include TUR of prostatic urethra
- Additional biopsies of any visible abnormality



EAU NMIBC Guidelines 2021

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The Value of Transurethral Bladder Biopsy after Intravesical Bacillus Calmette-Guérin Instillation Therapy for Nonmuscle Invasive Bladder Cancer: A Retrospective, Single Center Study and Cumulative Analysis of the Literature

J Urol (188)748-753, 2012

Natalia Swietek, Matthias Waldert, Maximilian Rom, Georg Schatzl, Helene G. Wiener, Martin Susani and Tobias Klatte*

From the Departments of Urology and Clinical Pathology (HGW, MS), Medical University of Vienna, Vienna, Austria

- 180 patients 2000-2011
- All high grade NMIBC (33% Ta, 56% T1, 11% Tis)
  - 73% concurrent Tis in cases with Ta/T1
- re-TURBT for all Ta/T1
- Repeat biopsy 4-6 weeks after induction BCG

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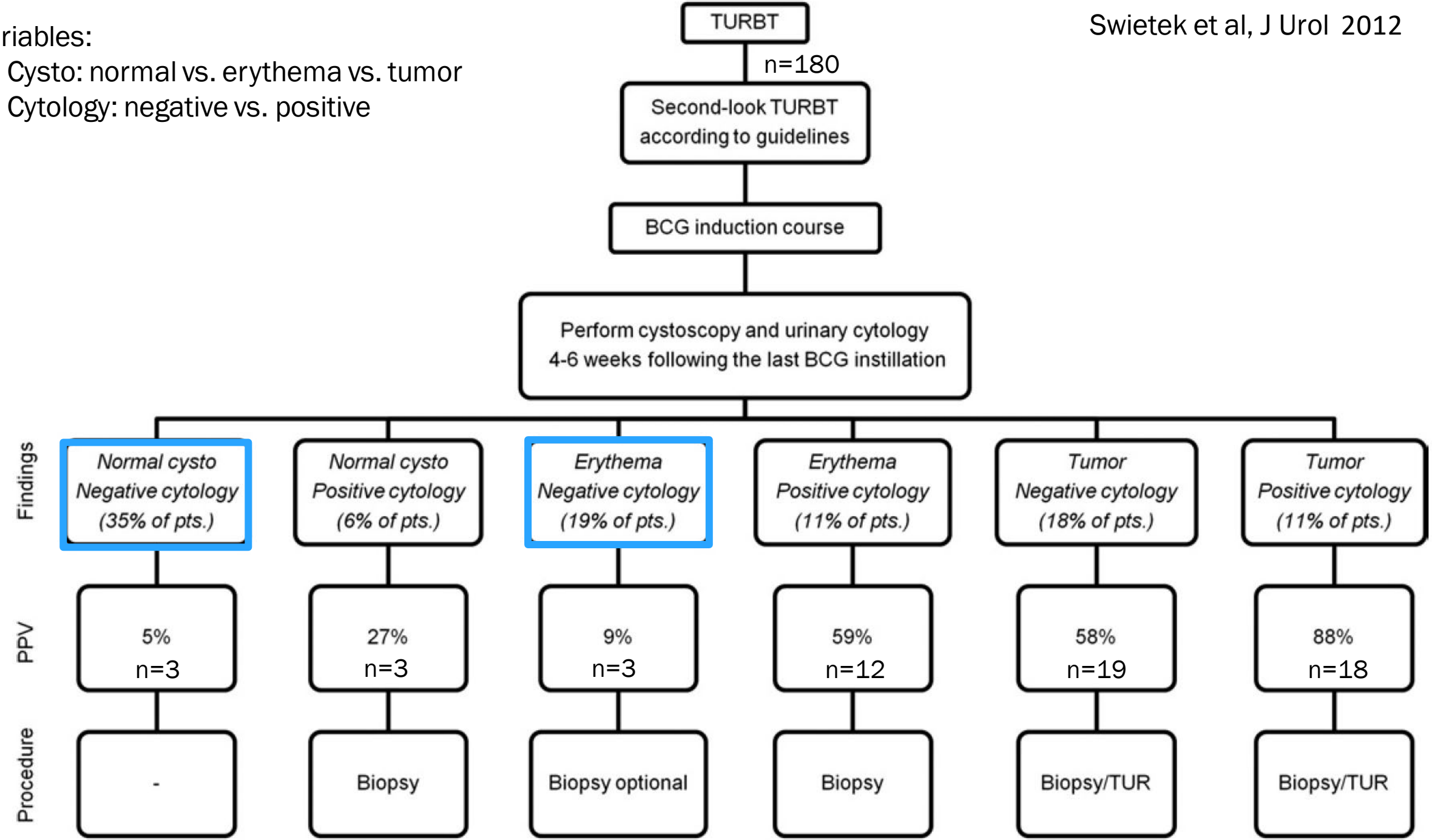
Variables:

- Cysto: normal vs. erythema vs. tumor
- Cytology: negative vs. positive

Swietek et al, J Urol 2012



Random Biopsies in BCG-unresponsive CIS

Nadofaragene trial:

- three patients in each cohort had CIS at the time of the protocol-mandated 12-month biopsy despite normal cystoscopy
  - one of these had suspicious urine cytology at month 3
- this represents 6 out of 104 recurrences in 150 patients
  - 3 out of 78 recurrences in 103 patients with CIS

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Boorjian et al, Lancet Oncol 2020

Detection of HG recurrence after BCG with blue light cystoscopy

- Multicenter Cysview Registry (n=1703)
  - Every patient mapped with WL + BL
- 282 patients within 12 mo of BCG
- 127 (45%) had high-grade recurrence
  - 13% (n=16/127) of recurrences detected by BL only
  - 6% (n=16/282) of cystos showed recurrence detected by BL only
- 14 of 16 patients with recurrence missed by WL had CIS

Caveats:

1. **Intermediate and high risk**
2. **Not all BCG-unresponsive**
3. **Not all patients biopsied**
4. **No random biopsies**

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Chappidi et al, J Urol 2021 (in press)

Detecting CIS - Summary

- Some CIS may be eradicated with TURBT
- We are missing CIS
  - Some Ta/T1 patients at study entry have occult CIS
  - Under-detection of CIS at time of surveillance
- BL and random biopsies increase detection of CIS at baseline and during surveillance
  - important for trial endpoints, although less relevant in RCT