What is success for CIS?

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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

\(\text{Some CRs in trials likely due to TURBT and not drug effect (similar to Ta/T1)}\)

\(^1\) 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

CIS was unifocal in 44% and multifocal in 56%

Mean: 1.9 lesions per patient

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

Lerner et al, Urol Oncol 2012
Table 2 – Natural history of carcinoma in situ treated only with biopsy/fulguration

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

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

<table>
<thead>
<tr>
<th></th>
<th>Pure CIS</th>
<th>CIS + Ta/T1</th>
<th>CIS + T1</th>
</tr>
</thead>
<tbody>
<tr>
<td>S1605</td>
<td>58%</td>
<td>42%</td>
<td>22%</td>
</tr>
<tr>
<td>Nado</td>
<td>76%</td>
<td>24%</td>
<td>5%</td>
</tr>
<tr>
<td>KN57</td>
<td>63%</td>
<td>37%</td>
<td>12%</td>
</tr>
<tr>
<td>QUILT</td>
<td>69%</td>
<td>31%</td>
<td>9%</td>
</tr>
</tbody>
</table>
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?
  - 20% if RC for NMIBC
  - 47% if RC for MIBC

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

**Note:** Roumiguié & Black, unpublished.
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
Other critical questions

- Timing of CR
- Criteria for CR: Cytology
- Criteria for CR: Mandatory Biopsy
- Consider impact of systemic vs local therapy
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 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
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
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
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

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

Swietek et al, J Urol 2012

TURBT

Second-look TURBT according to guidelines

BCG induction course

Perform cystoscopy and urinary cytology 4-6 weeks following the last BCG instillation

Findings

- Normal cysto
- Normal cysto
- Erythema
- Erythema
- Tumor
- Tumor

- Negative cytology (35% of pts.)
- Positive cytology (6% of pts.)
- Erythema (19% of pts.)
- Positive cytology (11% of pts.)
- Negative cytology (18% of pts.)
- Positive cytology (11% of pts.)

PPV

- 5% n=3
- 27% n=3
- 9% n=3
- 59% n=12
- 58% n=19
- 88% n=18

Procedure

- -
- Biopsy
- Biopsy optional
- Biopsy
- Biopsy/TUR
- Biopsy/TUR
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

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

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