AUA Summer School Webinar
Management of NMIBC:
Practical Solutions for Common Problems (2020)

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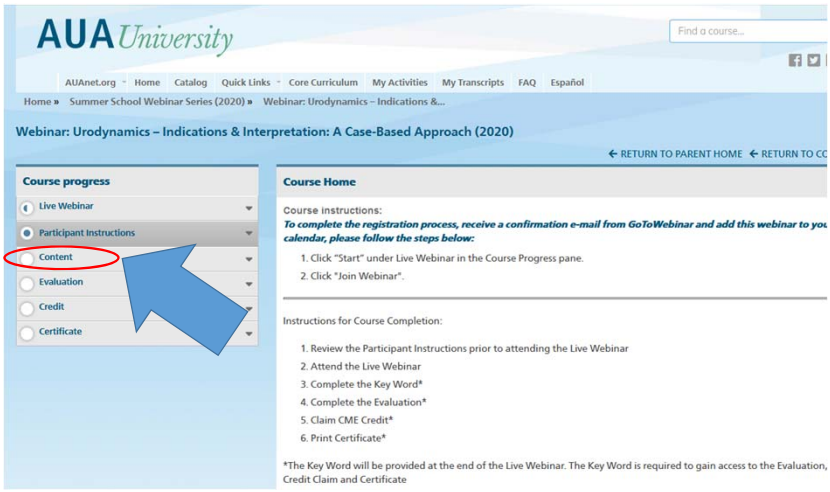

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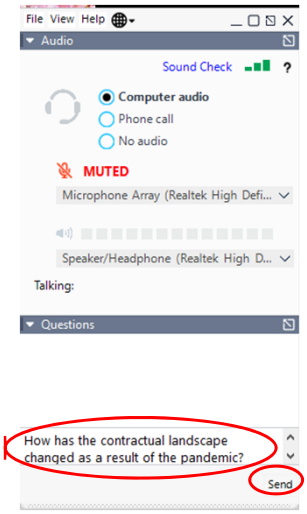
We Need YOU To Actively Participate!



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Acknowledgements

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Knowledge Assessment

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AUA Course Faculty

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Associate Professor of Urology

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Chair and Professor of Urology

Fred Witjes (Radbound, the Netherlands)
Professor of Urology

Ashish Kamat (MD Anderson Cancer Center)
Professor of Urology

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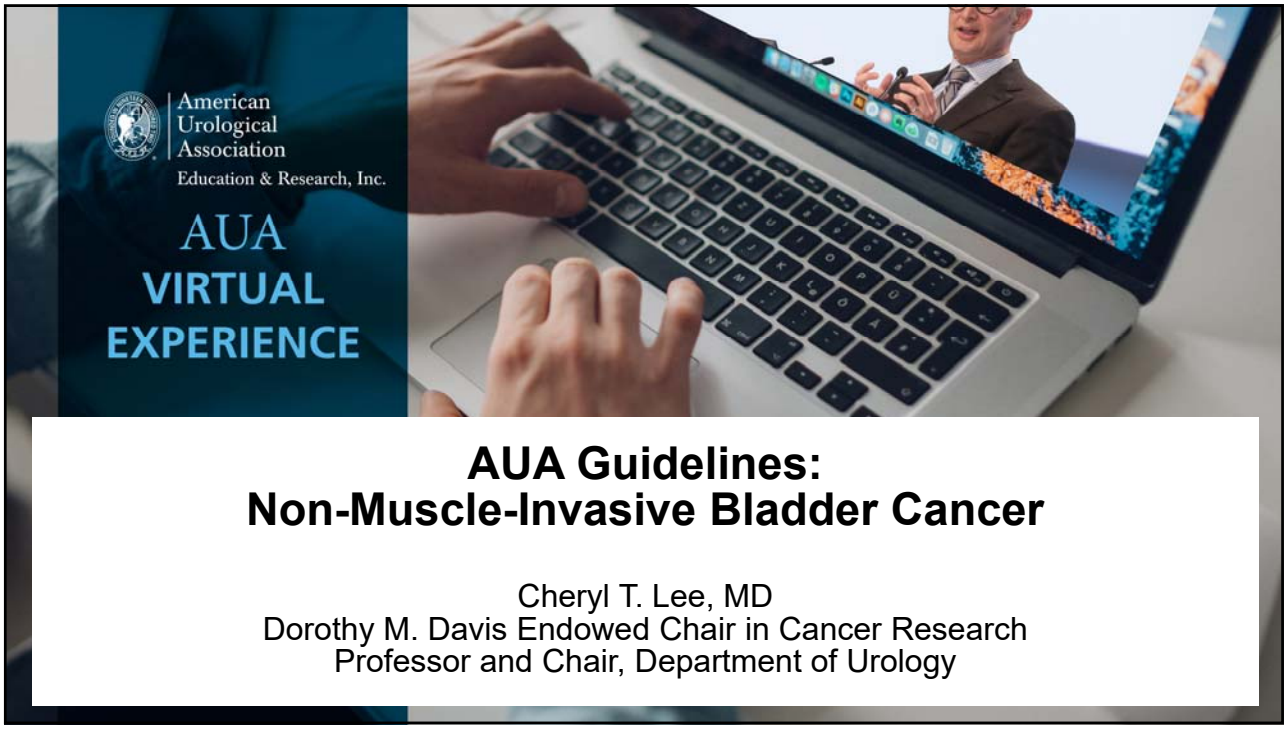
Learning Objectives

After participating in this course, attendees will be able to:

1. Implement current AUA NMIBC practice guidelines into the office setting.
2. Identify the best intravesical agent and duration of therapy for low, intermediate, and high-risk settings and what to do during a BCG shortage.
3. Identify methods to treat significant toxicities from various intravesical therapies.
4. Define high-risk scenarios that necessitate cystectomy and options for BCG-unresponsive disease.
5. Discuss the scientific rationale for investigating immune oncology agents for BCG unresponsive disease and become familiar with current clinical trial designs.



AUA Guidelines: Non-Muscle-Invasive Bladder Cancer

Cheryl T. Lee, MD
Dorothy M. Davis Endowed Chair in Cancer Research
Professor and Chair, Department of Urology

Disclosures

Consultant,
US Genitourinary Advisory Board
(Merck & Co)

Disclosures for Cheryl T. Lee, MD

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American Urological Association (AUA) Guideline

DIAGNOSIS AND TREATMENT OF NON-MUSCLE INVASIVE BLADDER CANCER: AUA/SUO GUIDELINE

Sam S. Chang, MD, MBA; Stephen A. Boorjian, MD; Roger Chou, MD; Peter E. Clark, MD; Siamak Daneshmand, MD; Badrinath R. Konety, MD, FACS, MBA; Raj Pruthi, MD, FACS; Diane Z. Quale; Chad R. Ritch, MD, MBA; John D. Seigne, MD; Eila Curlee Skinner, MD; Norm D. Smith, MD; James M. McKiernan, MD

Amended 2020

Chang, et al. JUrol 196 (4):1021–1029, 2016

TABLE 4: AUA Risk Stratification for Non-Muscle Invasive Bladder Cancer		
Low Risk	**Intermediate Risk**	**High Risk**
LG[a] solitary Ta ≤ 3cm	Recurrence within 1 year, LG Ta	HG T1
PUNLMP[b]	Solitary LG Ta > 3cm	Any recurrent, HG Ta
	LG Ta, multifocal	HG Ta, >3cm (or multifocal)
	HG[c] Ta, ≤ 3cm	Any CIS[d]
	LG T1	Any BCG failure in HG patient
		Any variant histology
		Any LVI[e]
		Any HG prostatic urethral involvement

[a]LG = low grade; [b]PUNLMP = papillary urothelial neoplasm of low malignant potential; [c]HG = high grade; [d]CIS=carcinoma *in situ*; [e]LVI = lymphovascular invasion

Chang, et al. JUrol 196 (4):1021–1029, 2016

American Urological Association

Guideline Statements (Diagnosis)

1. "At the time of resection of suspected bladder cancer, a clinician should perform a thorough cystoscopic examination of a patient's entire urethra and bladder that evaluates and documents tumor size, location, configuration, number, and mucosal abnormalities." (Clinical Principle)

2. At initial diagnosis of a patient with bladder cancer, a clinician should perform complete visual resection of the bladder tumor(s), when technically feasible. (Clinical Principle)

Chang, et al. JUrol 196 (4):1021–1029, 2016

10-Item TURBT Checklist Collaborative MSKCC (Herr and Anderson)

TURBT Quality Audit	
A high quality TURBT includes	
1. Obtaining the information necessary for accurate classification of clinical stage and cancer risk.	
2. Complete resection of all visible tumors and suspicious areas when safe, feasible and bladder preservation is planned.	
3. Careful assessment of bladder integrity after tumor resection	
Procedure Checklist	
Assessment of prognostic factors	**Acceptable responses**
1. Describe number of tumors	1, 2-5, >5, diffuse
2. Describe size of largest tumor	For reference: end of cutting loop is approximately 1 cm wide
3. Describe characteristics of tumors	Sessile, nodular, papillary, flat
4. Describe recurrent versus primary tumors	Recurrent, primary
5. Assess for presence of carcinoma *in situ*	Suspicious, not suspicious
6. Report 2010 AJCC clinical tumor stage	cTis, cTa, cT1, cT2, cT3, cT4
Intraoperative processes	
7. Bimanual exam under anesthesia	Yes, no
8. Visually complete resection	Yes, no
9. Visualization of detrusor muscle in resection base	Yes, no
10. Visual evaluation for perforation	Yes, no

Anderson, et al. J Urol, 2016;196(4):1014-20.

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The Checklist Improves Reporting of Critical TURBT Elements

Checklist item	Before checklist implementation	After checklist implementation
Describe tumor number	332 (78%)	303 (93%)
Describe tumor size	259 (61%)	286 (88%)
Describe tumor characteristics	292 (68%)	298 (92%)
Describe recurrent vs. primary tumor	192 (45%)	257 (79%)
Assess for presence of CIS	160 (37%)	259 (80%)
Report 2010 AJCC clinical tumor stage	77 (18%)	250 (77%)
Bimanual exam under anesthesia	194 (45%)	226 (70%)
Visually complete resection	270 (63%)	268 (82%)
Visualization of detrusor muscle in resection base	126 (29%)	222 (68%)
Visual evaluation for perforation	171 (40%)	237 (73%)

Anderson, et al. J Urol, 2016;196(4):1014-20

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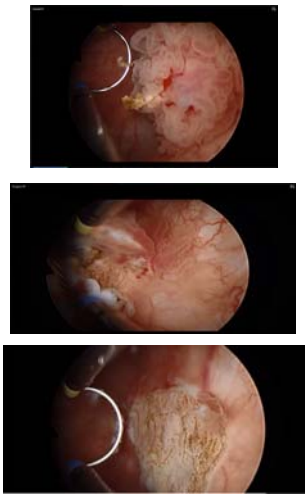
Why Consider TURBT Quality?

- Technical skill matters
- Staging
- Completeness of resection is the KEY
  - Better outcomes after intravesical therapy
  - Better outcomes after radiation therapy (TMT)
  - Higher pT0 with radical TURBT prior to neoadjuvant chemotherapy



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Guideline Statements (Diagnosis)

30. **<u>Enhanced Cystoscopy</u>**: In a patient with NMIBC, a clinician should offer **blue light cystoscopy** at the time of TURBT, if available, to increase detection and decrease recurrence. (Moderate Recommendation; Evidence Strength: Grade B)

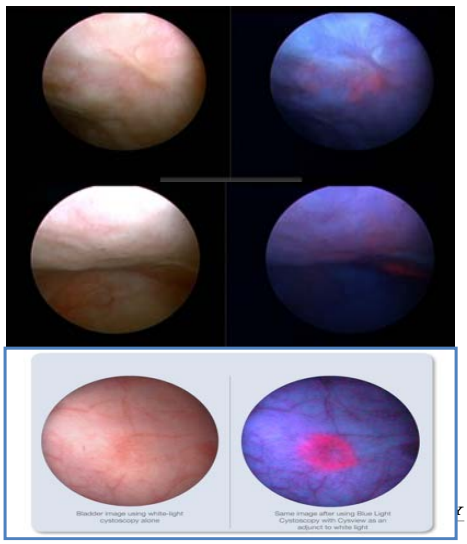
Chang, et al. JUrol 196 (4):1021–1029, 2016

The Ohio State University Wexner Medical Center

Blue Light Cystoscopy: Cysview Photo Dynamic Diagnosis

- Multicenter RCT's in US, Canada, and Europe
- Fluorescent cystoscopy increased detection of:
  - ↑ Ta tumors by 16%,
  - ↑ high-risk T1 tumors by 10-13%,
  - ↑ high-risk CIS lesions by 30-46%

  (Stenzl, 2010/ Grossman 2012).
- Med f/u ~4.5 years
  - median time to recurrence was 16.4 (blue light) versus 9.4 months (white light) (Grossman 2012)



Blue Light with Cysview: Flexible Cystoscopy

- Phase III Multicenter RCT
  - Compared blue and white light flexible cystoscopy with cysview
  - 304 BC patients with high risk of recurrence
- 103 / 304 underwent biopsy for suspicious lesion
  - 63 confirmed malignant
    - 13 of 63 (~21%) only seen with blue light ($p<0.0001$)
    - 26 of 63 (41%) were CIS
      - 9 of 26 (~35%) only seen with blue light ($p<0.0001$)
  - False positive rate ~9% for blue and white light
  - Blue light increases detection of tumors using flex cystoscopy

Daneshmand, et al. JUrol. 2018 May;199(5):1158-1165

The Ohio State University Wexner Medical Center

Guideline Statements: Urinary Markers after Diagnosis

Clinical Context	Guideline Statement: Suggested Practice	Strength of Rec
Surveillance of NMIBC (9)	Clinicians should not use urinary biomarkers in place of cystoscopic evaluation	Grade B
History of Low Risk BC and Normal Cysto (10)	Clinicians should not routinely use a urinary biomarker or cytology during surveillance	Expert Opinion
Response to therapy (11)	Clinicians may use biomarkers to assess response to intravesical BCG (UroVysion® FISH) and adjudicate equivocal cytology (UroVysion® FISH and ImmunoCyt™)	Expert Opinion

Chang, et al. JUrol 196 (4):1021–1029, 2016

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Guideline Statements: Restaging TURBT

Guideline Statement	Clinical Context	Strength of Rec
Variant Histology	Pursuing bladder preservation in a patient with **variant histology**	Expert Opinion
Restaging TURBT	**Incomplete initial resection** : re-TURBT of all remaining tumor if technically feasible	Grade B
Restaging TURBT	High-risk, high-grade Ta tumors: consider repeat transurethral resection	Grade C
Restaging TURBT	**T1 disease:** perform repeat TUR of the primary tumor site to include **muscularis propria**	Grade B

Chang, et al. JUrol 196 (4):1021–1029, 2016

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Variant Histology

- 7,500 – 18,000 cases annually (10-25% of cases)
- Discordance between TURBT and Cystectomy (39-47%)
- Worse outcomes / Upstaging at cystectomy / Variable responses to IVT
- Up to 44% of variants may be missed by non specialized pathologists
  - Lymphoepithelial
  - Plasmacytoid
  - Nested variant
  - Micropapillary
  - Small cell histology

Abd El-Latif, et al JUrol 2013
Shah, RB Urol Onc 2012

Restaging TURBT

- Recommended **within 2-6 weeks** in the patient with uncertain resection.
- Up to 29% of patients **upstaged**
- Rates of **residual tumor** detected by the second TURBT are 55-76%
  - When muscle in the specimen residual tumor ~20%
  - When absent, residual tumor rate >50%
- Roughly **1/3 of cases** will have a **change** in **the treatment** plan

Miladi M, et al. European Urology 2003; 43:241-245.
Huang J et al, Urol Int 89 (2012); Herr HW. J Urol, 1999; 162:74-76.

available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Review – Bladder Cancer

Repeat Transurethral Resection in Non–muscle-invasive Bladder Cancer: A Systematic Review

Screened 15,209 manuscripts; selected 31 (8409 pts HG Ta/T1)

- At reTUR:
  - For Ta: residual tumor 17-67%; upstaging 0-8%
  - For T1: residual tumor 20-71%; upstaging 0-32%
- Clear Recurrence Benefit for Ta: 16% (reTUR) vs 58% (no-reTUR)
  - No clear trend for T1 (range 18-56%)
- **Benefits for progression and overall survival are not clear**

Cumberbatch, et al. EUROPEAN UROLOGY 73 (2018) 925 – 933

Guideline Statements: Risk Adjusted Surveillance

Risk Category	Clinical Context	Strength of Rec
Low (33)	First surveillance cystoscopy is negative: cysto in 6-9 mos, then annually. ?d/c after 5 years free of recurrence	Grade C
Low (34)	If asymptomatic , *no routine upper tract surveillance*	Expert Opinion
Intermediate (36)	First surveillance cystoscopy is negative: Cysto + cytol every 3-6 mos X 2 years, every 6-12 mos X 2 years, and then annually. *Upper tract imaging every 1-2 years*	Expert Opinion
High (37/38)	First surveillance cystoscopy is negative : Traditional surveillance (cysto +cytology) of bladder with *upper tract imaging every 1-2 years*	Expert Opinion

Chang, et al. JUrol 196 (4):1021–1029, 2016

The Ohio State University
Wexner Medical Center

Take Home Points

- The 2016 AUA Guidelines (with 2020 updates) address many areas of common practice and are based on evidence and expert opinions, when evidence is limited
- The guidelines strive to offer diagnostic, therapeutic, and surveillance recommendations that are risk-stratified
- The guidelines should be integrated into your clinical practice to optimize patient outcomes

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AUA 2020 summer course, practical management of NMIBC

AUA vs. EAU risk classification, guideline treatments

prof. Fred Witjes, UMC Nijmegen, the Netherlands
Thursday, July 30, 2020

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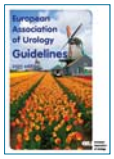

Radboudumc

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Conflicts of interest after 2017

(not relevant for this lecture)

Company	Advisor/lecturer (last year)
BeiGene	2020
Janssen	2020
OncoDiag	2020
Astellas	2020
Nucleix	2019
Ipsen	2019
BMS	2019
MSD	2019
Sanofi	2019
Roche	2018
Tocagen	2018

Start with a good TUR (both diagnostic ánd therapeutic)!!

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Guideline risk groups:

AUA 2016 and EAU 2020 are similar

Risk groups

American Urological Association 2016

European Association of Urology Guidelines 2020

Risk group	AUA definition	EAU definition (grade B)
Low	LG solitary Ta ≤3cm PUNLMP	Primary, solitary, Ta, G1 or low grade, <3cm, no CIS

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Risk groups

American Urological Association 2016

European Association of Urology Guidelines 2020

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Low	LG solitary Ta ≤3cm PUNLMP	Primary, solitary, Ta, G1 or low grade, <3cm, no CIS
High	HG T1 Recurrent or >3m HG Ta CIS BCG failures Variant histology LVI, PU involvement	Any of: - T1 - G3 or high grade - CIS - multiple **and** recurrent **and** >3cm TaG1G2 tumors

Risk groups

American Urological Association 2016

2020

Risk group	AUA definition	EAU definition (grade B)
Low	LG solitary Ta ≤3cm PUNLMP	Primary, solitary, Ta, G1 or low grade, <3cm, no CIS
Intermediate	LG Ta: - recurrence <1 year - Solitary >3 cm - Multifocal HG Ta ≤3cm or LG T1	The rest
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American Urological Association 2016

2020

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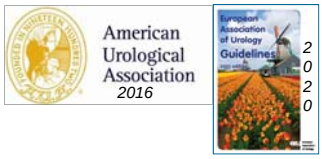
Low	LG solitary Ta ≤3cm PUNLMP	Primary, solitary, Ta, G1 or low grade, <3cm, no CIS
Intermediate	LG Ta: - recurrence <1 year - Solitary >3 cm - Multifocal **HG Ta ≤3cm or LG T1**	The rest
High	HG T1 Recurrent or >3m HG Ta CIS **BCG failures** **Variant histology** **LVI, PU involvement**	Any of: - T1 - G3 or high grade - CIS - multiple **and** recurrent **and** >3cm TaG1G2 tumors

Highest risk



- AUA
  - No separate definition
- EAU Definition, any of:
  - T1G3 associated with concurrent bladder CIS
  - multiple and/or large T1G3 and/or recurrent T1G3
  - T1G3 with CIS in prostatic urethra
  - some forms of variant histology
  - T1 with lymphovascular invasion

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Better predictors or….

risk group sub-classification

Differentiation intermediate risk *(Kamat, 2014)*

- Aim: IR traditionally poorly defined ("the rest")
- M&M: literature review IR-NMIBC literature and guidelines

- Results: Current definitions and management recommendations for IR vary considerably
- Additional factors for clinical decisions in IR disease:
  - number of tumors (1 vs. greater than 1)
  - size (<3 cm vs. >3cm)
  - timing recurrence (within or after 1 year)
  - Frequency of recurrence (≤1 vs. >1 per year)

→ 4 factors used for sub classification of "the rest"

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Additional bad factors in high risk

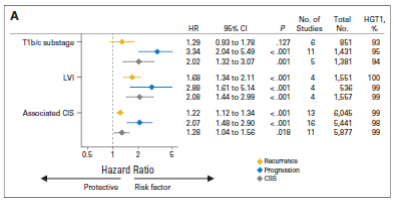
Improving Selection Criteria for Early Cystectomy in High-Grade T1 Bladder Cancer: A Meta-Analysis of 15,215 Patients

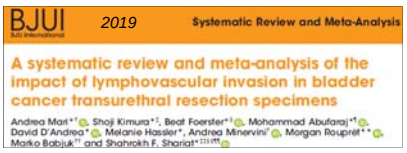
William Martin-Doyle, Jeffrey J. Leow, Anna Orsola, Steven L. Chang, and Joaquim Bellmunt

JOURNAL OF CLINICAL ONCOLOGY

Published Ahead of Print on January 5, 2015

- At 5 years
  - Recurrences 42%
  - Progression 21%
  - CSM 13%
- **Most important risk factor T1b/c**
  - progression: HR = 3.34
  - CSM: HR = 2.02
- And
  - **LVI**
  - **CIS**
  - Non-BCG (intervention, not risk)
  - Size >3cm
  - Older age




BJUI 2019 Systematic Review and Meta-Analysis

A systematic review and meta-analysis of the impact of lymphovascular invasion in bladder cancer transurethral resection specimens

Andrea Mari*†, Shoji Kimura*‡, Beat Foerster*†, Mohammad Abufaraj*†, David D'Andrea*, Melanie Hassler*, Andrea Minervini*, Morgan Roupret*†, Marko Babjuk†† and Shahrokh F. Shariat*‡‡§§

Pathology NMIBC: 2020 AUA abstracts

- T1 **subclassification** (<u>not in the guidelines!</u>)
  - MP72-02 (Cleveland)
    - 79 superficial T1 vs. 20 advanced T1 and 55 T2
      - Advanced T1 worst (!) 5 year survival
        - **Advanced T1 28%**
        - Superficial T1 68%
        - T2 49%
  - MP72-04 (Taiwan)
    - 138 focal T1 vs. 225 extensive T1
      - extensive defined as >1 mm lamina propria invasion
    - **Extensive T1 worse PFS**: HR 1.95
      - However, similar CSS

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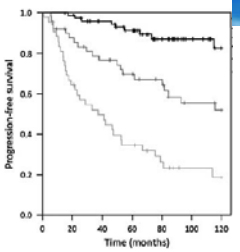
Markers for risk classification……..

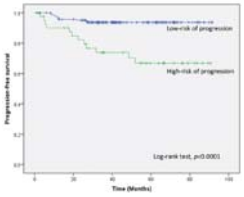
- Guideline considers prognostic markers promising
- Complex and not yet suitable for routine practice

- Beukers: 2015:
  - better PFS with low **methylation** rates
  - 3 molecular risk groups: 5 year PFS 8% vs 29% vs 63%

- Ingelmo 2017
  - regression analysis identified 2 **miRNAs** predicting:
    - tumor progression: HR 5.2 (2.2-12.0)
    - CSS: HR 3.9 (1.1-13.4)

- **But: results need external validation**





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Markers for risk classification……..

FUTURE
JUST AHEAD

- Guideline considers prognostic markers promising
- Complex and not yet suitable for routine practice

- Beukers: 2015:
  - better PFS with low **methylation** rates
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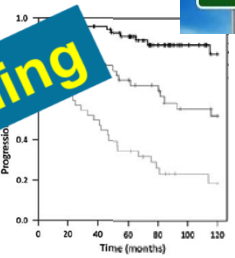
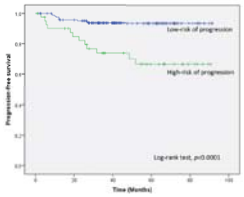
- **But: results need external validation**

Epigenetics are coming





Why are epigenetics important for BCa

- Current high-throughput sequencing makes research easier and results better
- Body of literature is growing exponentially

- Epigenetic changes are frequent in (urological) cancers, a.o. (N)MIBC, both in tissue and urine, and might be usefull in
  - Diagnosis
  - Prognosis
  - Potential targets for therapy since some of these changes are reversible

- **So, keep epigenetics in mind**

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Treatment recommendations according to risk category

Guideline treatment recommendations

General recommendations	Strength rating
Counsel smokers with confirmed non-muscle-invasive bladder cancer (NMIBC) to stop smoking.	Strong

AUA abstracts 2020: PD50-05 & PD41-11 (NY and Rochester):
BCa carcinogens are present in **E-cigarettes!**

Etiology

Risk factors. Multiple factors are associated with bladder carcinogenesis; however, tobacco smoking is the most significant and most common risk factor.[11] Although smoking cessation may somewhat decrease carcinogenesis risk, former smokers still have a higher risk of bladder cancer than those who never smoked.[11]

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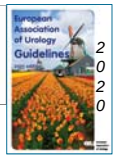
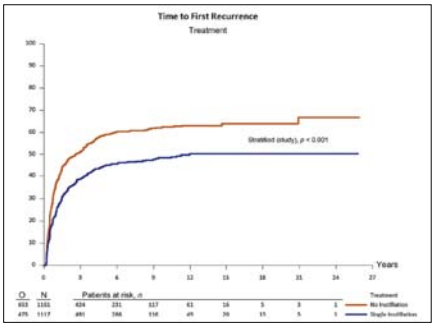
Low risk therapy advise

American Urological Association 2016

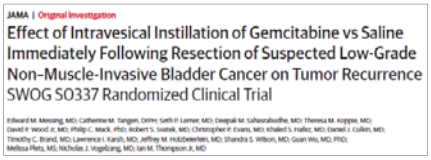


- AUA
  - In suspected or known low-risk, consider **SPI** chemo within 24 hours, except suspected perforation or extensive resection. (Moderate Recommendation; Evidence Strength: Grade B)
  - In a low-risk patient, **do not administer induction** intravesical therapy. (Moderate Recommendation; Strength of Evidence Grade C)
- EAU
  - **One immediate instillation** of chemotherapy (strong)

Low risk



- Update systematic review *(Sylvester, Eur Urol 2016)*
  - 11 studies and 2278 pts
  - Individual patient data meta-analysis
  - SPI reduces 5 year recurrence rate from **58.8% tot 44.5%** (p<0.001)
  - Not in pts with >1 prior recurrences per year of EORTC risk score ≥5
  - Overall survival 12.0% versus 11.2% due to EORTC score ≥ 5 pts.
- Conclusion: effective, but predominantly in real low risk cases

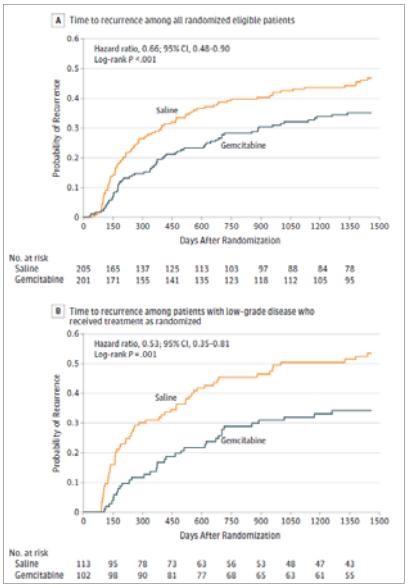

JAMA | Original Investigation

Effect of Intravesical Instillation of Gemcitabine vs Saline Immediately Following Resection of Suspected Low-Grade Non-Muscle-Invasive Bladder Cancer on Tumor Recurrence
SWOG S0337 Randomized Clinical Trial

- M&M: RCT, double blind, suspected low-grade NMIBC and without >2 low-grade UC episodes within last 18 months
- Th/ 1 hour gemcitabine (2g/100mL, n = 201) or saline (n = 205)
- Results
  - 383/406 pts completed trial
  - 4 year recurrence estimates: **35% vs. 47%** (HR 0.66; 0.48-0.90)
  - In low grade (n=215) 4 year recurrence estimates: 34% vs. 54% (HR 0.53; 0.35-0.81)
  - No grade 4 or 5 AE's, no significant differences in grade 3 or lower AE's
- Conclusion: SPI gemcitabine significantly reduced 4 year RR.
- Further research needed comparing gemcitabine with other agents

Table 3. Adverse Events Reported Among Patients Who Underwent TURBT and Received Instillation[a]

	No. of Events			
	Gemcitabine Group (n = 165)		Saline Group (n = 175)	
Adverse Events	Grade 1-2	Grade 3	Grade 1-2	Grade 3
Voiding dysfunction	31	0	32	3
Voiding pain/sexual pain	26	0	23	2
Hematuria	12	3	14	1
Gastrointestinal	8	0	4	0
Hematologic	5	0	5	0
Flu-like/other syndromes	3	0	4	0
Pain (not urologic or gastrointestinal)	5	0	1	0
Allergy/dermatologic	4	0	2	0
Genitourinary infection/perforation	1	0	4	0
Metabolic/mood alteration	2	0	1	0
Infection/pulmonary	0	1	1	0
Maximum grade, No. of patients	53	4	47	6



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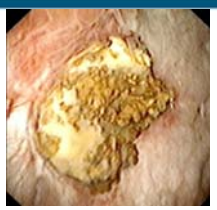
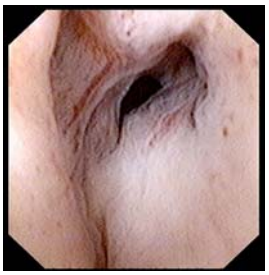
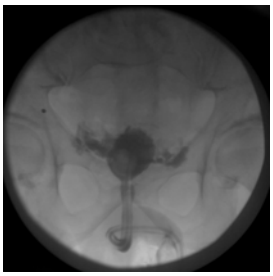
One instillation remarks



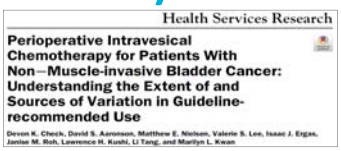
- Instillation should be given day of surgery
- All drugs seem equally effective
- Beware of a TUR perforation (check wat goes in and comes out!)





SPI (single postoperative instillation)

- Not always done due to many right and wrong reasons
- But: it is VERY **safe**


Health Services Research

Perioperative Intravesical Chemotherapy for Patients With Non–Muscle-invasive Bladder Cancer: Understanding the Extent of and Sources of Variation in Guideline-recommended Use

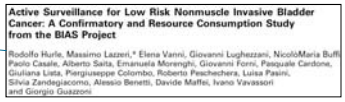
Devon K. Check, David S. Aaronson, Matthew E. Nielsen, Valerie S. Lee, Isaac J. Ergas, Janise M. Roh, Lawrence H. Kushi, Li Tang, and Marilyn L. Kwan

- **Alternatives**
  - Continuous bladder **irrigation** with saline for 24 hours
  - **Active surveillance** in case of low risk
  - Office **fulguration** (new in 2019 EAU guideline)


REVIEW

Meta-analysis of efficacy and safety of continuous saline bladder irrigation compared with intravesical chemotherapy after transurethral resection of bladder tumors

Zhongbao Zhou · Shikai Zhao · Youyi Lu · Jtao Wu · Yongwei Li · Zhenli Gao · Diandong Yang


Active Surveillance for Low Risk Nonmuscle Invasive Bladder Cancer: A Confirmatory and Resource Consumption Study from the BIAS Project

Rodolfo Hurle, Massimo Lazzeri, Elena Vanni, Giovanni Lughezzani, NicolòMaria Buffi, Paolo Casale, Alberto Saita, Emanuela Morenghi, Giovanni Forni, Pasquale Cardone, Giuliana Lista, Piergiuseppe Colombo, Roberto Peschechera, Luisa Pasini, Silvia Zandegiacomo, Alessio Benetti, Davide Maffei, Ivano Vavassori and Giorgio Guazzoni

Outpatient fulguration or laser vaporisation of small papillary recurrences can be used in patients with a history of TaG1/LG tumours.	Weak

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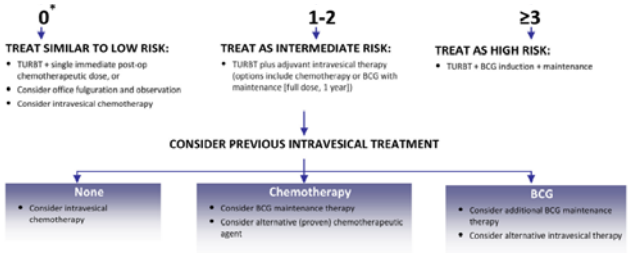
Interm. risk therapy advise

American Urological Association 2016

- **AUA**
  - In suspected or known intermediate-risk, consider SPI chemo within 24 hours, except suspected perforation or extensive resection. (Moderate Recommendation; Evidence Strength: Grade B)
  - In intermediate-risk consider a six week course of induction intravesical chemotherapy or immunotherapy. (Moderate Recommendation; Evidence Strength: Grade B)
  - In CR after induction chemo/BCG, consider maintenance therapy as tolerated. (Evidence Strength: Grade C)
- **EAU**
  - SPI of chemo followed by further instillations (A)
    - Either chemotherapy for a maximum of 1 year
    - Or 1 year of full dose BCG (less recurrences, more toxicity)

Practice issue: differentiate IR *(Kamat, J Urol 2014)*

- This is the largest group in daily practice
- Treatment based on number of risk factors:
  - number of tumors (1 vs. greater than 1)
  - size (<3 cm vs. >3cm)
  - timing recurrence (within or after 1 year)
  - Frequency of recurrence (≤1 vs. >1 per year) number of tumors (greater than 1)



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High risk therapy advise

American Urological Association 2016

European Association of Urology Guidelines 2020

- AUA
  - In newly diagnosed CIS, HG T1 or Ta (re-TUR!) administer a six-week induction course of **BCG**. (Strong Recommendation; Evidence Strength: Grade B); responders **3 years** maintenance (Moderate Recommendation; Evidence Strength: Grade B)

- EAU
  - SPI grade C recommendation
  - Intravesical full dose BCG instillations for **1 to 3 years** (strong)
    - The additional beneficial effect of the 2nd and 3rd year should be weighed against its added **costs** and **inconveniences**.

Beyond the guidelines:

BCG shortage in high risk disease

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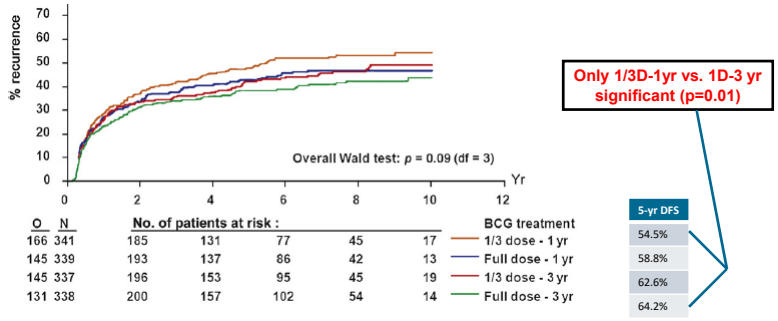
EORTC 30962 *(Oddens 2013)*



- Intermediate risk: 1 year full dose
- High risk: 3 years full dose (depending on toxicity and costs)

- **Toxicity and progression and CSM same!!**

Options to "save" BCG *(Mostafid et al, Eur Urol 2015)*

- Safe options
  - 1 year maintenance, not 3 (more recurrences, not more progression)
  - 2 instead of 3 maintenance treatments (1 is not enough)
  - Maintenance with 1/3 dose (more recurrences, not more progression)

  - CIS: maintenance 3 years (1 year full dose, 1/3 dose year 2 and 3)

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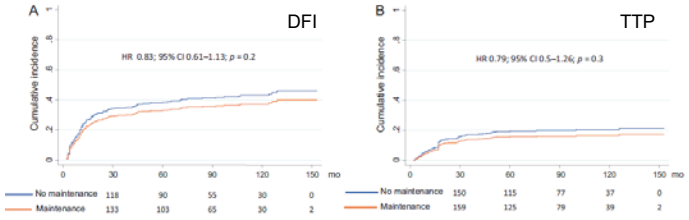
Options to "save" BCG *(Mostafid et al, Eur Urol 2015)*

- Safe options
  - 1 year maintenance, not 3 (more recurrences, not more progression)
  - 2 instead of 3 maintenance treatments (1 is not enough)
  - Maintenance with 1/3 dose (more recurrences, not more progression)

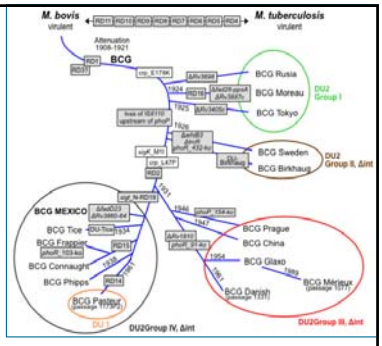
  - CIS: maintenance 3 years (1 year full dose, 1/3 dose year 2 and 3)

CUETO 98013 *(Martinez-Pineiro 2015)*

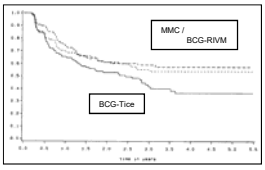
- BCG induction vs. BCG induction and 1 instillation per 3 months for 3 years.
- 397 high risk NMIBC patients treated
  - 5 year RR (33.5% and 38.5%) and 5 year progression (16% and 19.5%) similar
  - Toxicity similar



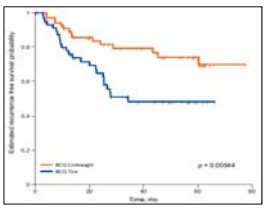
Does the BCG strain matter?



- Vegt et al, J Urol 1995
  - BCG **Tice** vs. BCG **RIVM** vs. MMC
    - 6 weeks BCG vs. 6 months (n=9) MMC
  - 437 intermediate and high risk NMIBC pts.
  - BCG RIVM and MMC equally effective
  - BCG Tice more recurrences (p=0.01)



- Rentsch et al, Eur Urol 2014
  - Investigator initiated trial
  - BCG **Tice** vs. **Connaught**
  - 142 pts. Randomized
  - BCG Tice more recurrences (p=0.01)
  - In mice Connaught stronger immune response



Highest risk therapy advise

- Very high risk
  - In persistent or recurrent HG Ta or CIS after BCG offer a **second course** of BCG. (Moderate Recommendation; Strength of Evidence C)
  - In a fit patient with HG T1 after BCG induction, or T1 tumors with CIS, LVI, or variant histologies, offer radical **cystectomy**. (Moderate Recommendation; Evidence Strength: Grade C)
- BCG unresponsive
  - unwilling or unfit for cystectomy clinical trial enrollment is recommended or intravesical chemo when **clinical trials** are unavailable.

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Highest risk therapy advise

- Very high risk
  - **cystectomy** should be considered (C)
- BCG unresponsive
  - **Recommendation: perform a radical cystectomy**
  - In patients not candidates for RC due to comorbidities use **preservation strategies** (weak)
    - intravesical chemotherapy
    - chemotherapy and microwave-induced hyperthermia.
    - Experience is limited

Treatment options in BCG unresponsive disease

→ Dr Kamat

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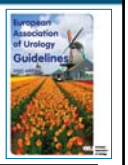
BCG failure: EAU guideline alternatives



- In patients not candidates for RC due to comorbidities use preservation strategies (weak)
  - intravesical **chemotherapy** (gemcitabine ± docetaxel)
  - **microwave-induced chemo-hyperthermia**
  - **EMDA**
    - BCG + EMDA/MMC (Recent Cochrane review, Jung 2017)
  - Intravesical or systemic **immunotherapy**, preferably within clinical trials.

Multi-Institution Evaluation of Sequential Gemcitabine and Docetaxel as Rescue Therapy for Nonmuscle Invasive Bladder Cancer

J Urol May 2020

Ryan L. Steinberg, Lewis J. Thomas, Nathan Brooks, Sarah L. Mott, Andrew Vitale, Trafford Crump, Mounica Y. Rao, Marcus J. Daniels, Jonathan Wang, Supriya Nagaraju, William C. DeWolf, Donald L. Lamm, Max Kates, M. Eric Hyndman, Ashish M. Kamat,* Trinity J. Bivalacqua, Kenneth G. Nepple and Michael A. O'Donnell†,‡

Take home messages 1

- Initial therapy
  - A good and complete TUR is important for diagnosis and prognosis, consider the re-TUR
- Prognosis
  - Use risk groups for different therapies in NMIBC patients
  - Remember additional risk factors
    - e.g. subclassification in intermediate risk
    - e.g. pT1b in high risk….
    - Future: epigenetics

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Take home messages 2

- Additional therapy
  - SPI is effective and safe and enough in low risk patients
    - SPI not always done nor always feasible
  - In intermediate risk patients use an adequate course of chemotherapy or 1 year of BCG
    - Try to subclassify the intermediate risk group
  - In high risk patients or CIS use full dose (3 years) maintenance BCG
    - Know BCG shortage options (chemo, dose reduction etc)
  - In highest risk patients and BCG unresponsive consider cystectomy
    - **Alternatives** are gem/docetaxel and intravesical RF induced thermo-chemotherapy, although results should be interpreted with care

So know and follow the guideline(s)……

- Ritch et al, J Urol 2020 (398 patients, 2001-2017)
  - The AUA/SUO NMIBC risk classification appropriately stratifies into a likelihood of recurrence and progression. **It should be used** at diagnosis to counsel patients and guide therapy
- Tobert et al, Urology 2019 (847 patients, 1992-2009 with high grade NMIBC)
  - **Overall compliance with AUA guidelines was <1%**, and did not markedly improve over study period
  - Compliance was not associated with cancer-specific survival
- Datovo et al, WJUrol 2019 (198 patients, 2005-2016)
  - **Non-adherence** to follow-up cysto's in NMIBC is associated with **more than twice progression risk**

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Thank you for your attention

Options after Failure of BCG Therapy When Should We Move to Cystectomy?

ASHISH M. KAMAT, MD, MBBS, FACS

PROFESSOR OF UROLOGIC ONCOLOGY
WAYNE B. DUDDLESTEN PROFESSOR OF CANCER RESEARCH
PRESIDENT, INTERNATIONAL BLADDER CANCER GROUP (IBCG)
ASSOCIATE CANCER CENTER DIRECTOR, RFHNH

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center Making Cancer History®

When Should We Move to Cystectomy in NMIBC?

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center Making Cancer History®

Short Answer

- In a patient with NMIBC, we should move to radical therapy (radical cystectomy in this case)
- When NOT removing the bladder would present a loss of an opportunity to CURE the patient

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AUA Guidelines

Role of Cystectomy in NMIBC

28. In a high-risk patient who is fit for surgery with persistent high-grade T1 disease on repeat resection, or T1 tumors with associated CIS, LVI, or variant histologies, a clinician should consider offering initial radical cystectomy. (Moderate Recommendation; Evidence Strength: Grade C)

https://www.auanet.org/education/guidelines/non-muscle-invasive-bladder-cancer.cfm

Key Fact

Intravesical Therapy is not a substitute for Bad Judgment

IMPORTANT DRUG WARNING

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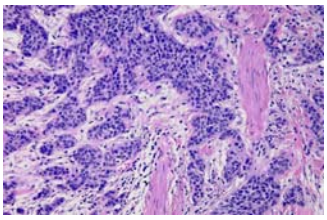
Key Fact

- T1HG is not a superficial cancer



Key Fact

- T1HG is not a superficial cancer

T1 HG = cT3b
Gleason 5+5
12/12 Positive Cores
PSA 75

Ferguson & Kamat, Urol Onc, 2018

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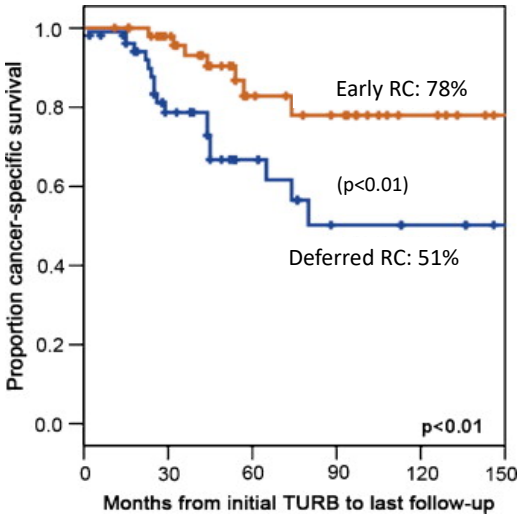
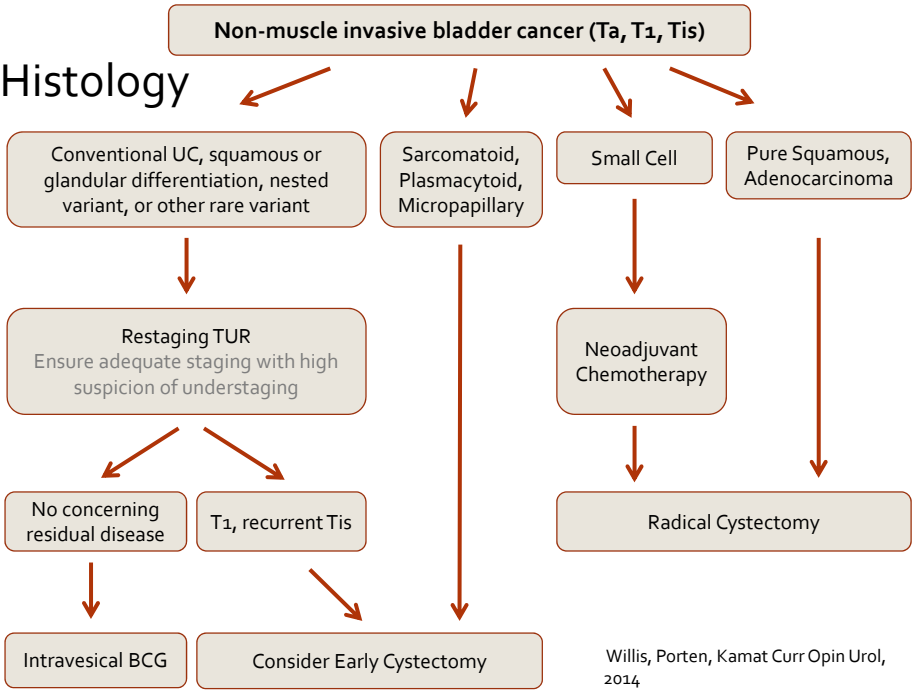
Immediate vs Deferred Cystectomy for T1HG

10 yr Cancer Specific Survival



Denzinger Eur Urol, 2007

Variant Histology



Willis, Porten, Kamat Curr Opin Urol, 2014

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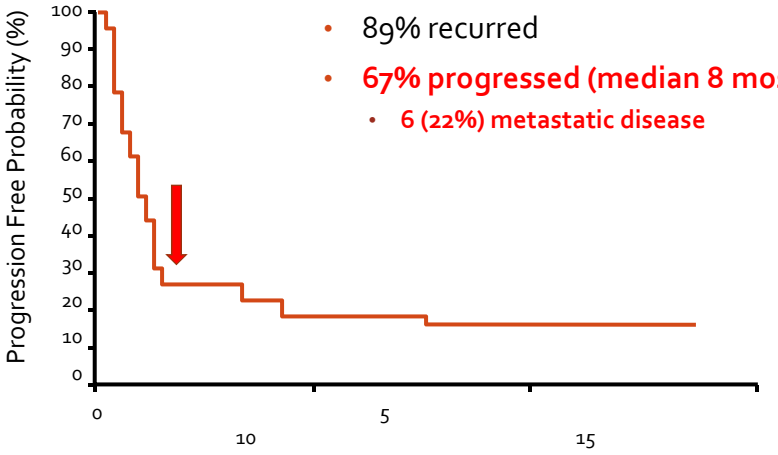
Micropapillary Bladder Cancer

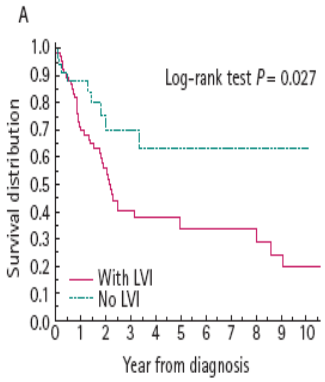
High Progression rate despite Intravesical BCG



- 89% recurred
- **67% progressed (median 8 mos)**
  - **6 (22%) metastatic disease**

Kamat AM et al, J Urol, 2006; Kamat AM et al Cancer, 2007; Willis et al J Urol, 2015

LVI in TURBT



Streeper NM et al, 2008

LVI on TURBT associated with

- Lower 5-year DSS
  - 34% vs 63% (p=.027)
- Trend towards understaging
  - LVI 75% vs 46% (p=.08)

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AUA Guidelines

Role of Cystectomy in NMIBC

Initial Radical Cystectomy should be offered to any fit patient who has
T1HG on repeat TUR
T1HG with CIS
LVI
Variant histology

https://www.auanet.org/education/guidelines/non-muscle-invasive-bladder-cancer.cfm

AUA Guidelines

Role of Cystectomy in NMIBC

29. In a high-risk patient with persistent or recurrent disease within one year following treatment with two induction cycles of BCG or BCG maintenance, a clinician should offer radical cystectomy. (Moderate Recommendation; Evidence Strength: Grade C)

https://www.auanet.org/education/guidelines/non-muscle-invasive-bladder-cancer.cfm

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Classification of BCG Failure

BCG refractory:	Persistent HG disease at 6 months despite adequate BCG. Also includes any stage/grade progression by 3 months after iBCG cycle (i.e., T1HG at 3 months after initial Ta, or CIS).
BCG relapsing:	Recurrence of HG disease after achieving a disease-free state at 6 months following adequate BCG. Previously been subdivided based on time to recurrence after stopping BCG (i.e., early [< 12 months], intermediate [1-2 years] or late [> 24 months])
BCG intolerant:	Disease persistence due to inability to receive adequate BCG* due to toxicity.

Kamat AM, et al. *J Clin Oncol.* 2016;34(16):1935-44.

Classification of BCG Failure

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BCG intolerant:	Disease persistence due to inability to receive adequate BCG* due to toxicity.
BCG unresponsive:	BCG refractory + BCG relapsing disease (within 6- 12 months of last BCG exposure) Meant to denote a subgroup of patients at highest risk of recurrence and progression for whom additional BCG therapy is not a feasible option. These patients can be considered for single arm studies.

Kamat AM, et al. *J Clin Oncol.* 2016;34(16):1935-44.

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Definition of BCG Unresponsive Disease

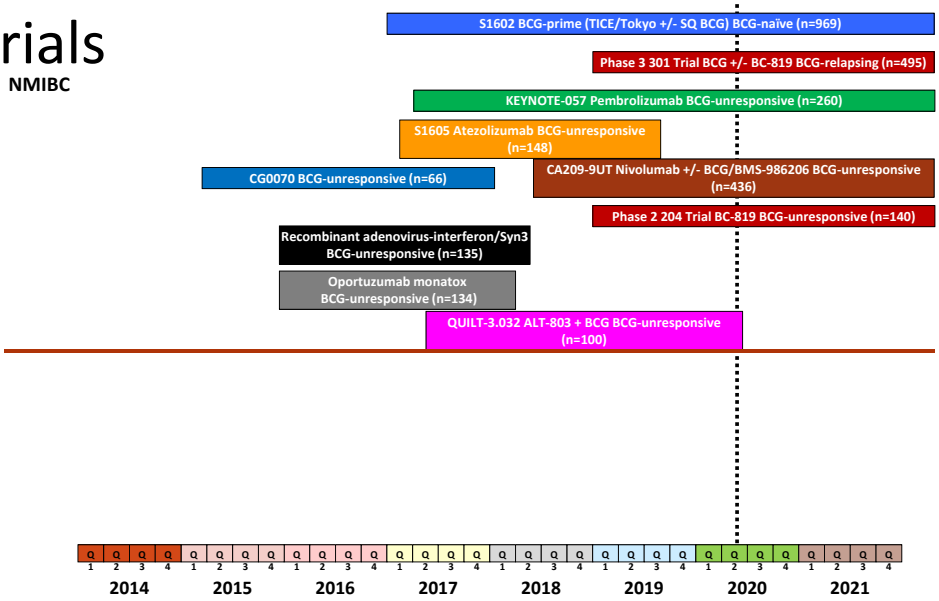
- Persistent or new **T1 HG** disease
  - at first evaluation (3 mos) following induction BCG
- Persistent or recurrent **CIS**
  - within 12 months of completion of adequate BCG therapy
- Recurrent **HG Ta/T1** disease
  - within 6 months of completion of adequate BCG therapy

Adequate BCG therapy defined as:
at least 5 of 6 doses of iBCG + at least 2 additional doses of mBCG

Kamat et al, JCO, 2016; Lerner et al, Bladder Cancer, 2016, FDA Guidance Document, 2018

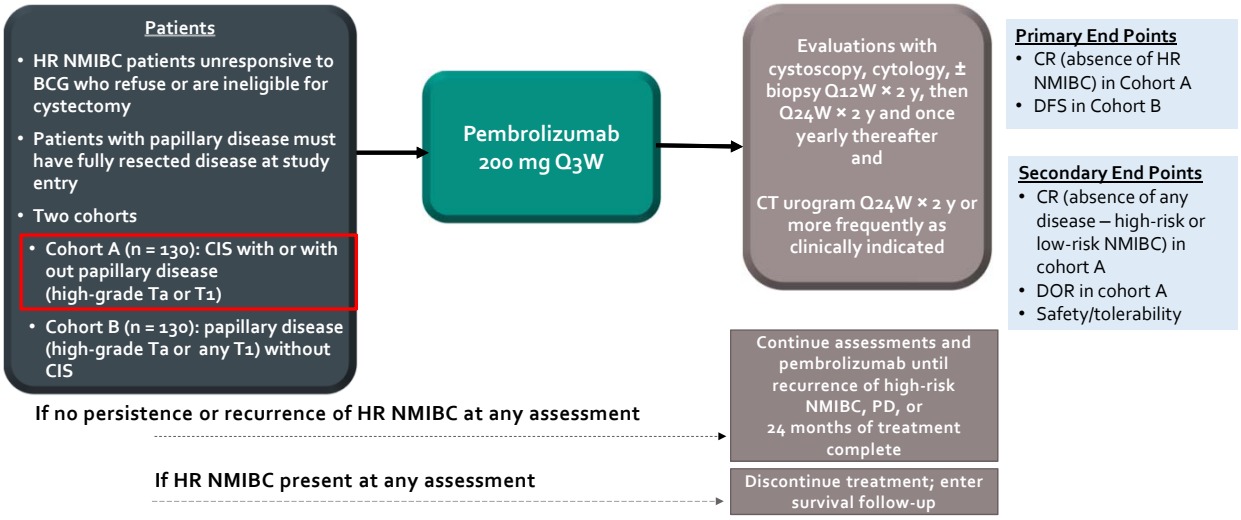
Early Stage UC Registration Trials

NMIBC



Noah Hanh, UroToday

KEYNOTE-057: Single-Arm, Open-Label Phase 2 Study (NCT02625961)



ASCO 2019

Key Baseline Characteristics KN057

Characteristic	N=96
Median age, years (range)	73 (44-92)
<65	30 (31.3)
≥65 to <75	24 (25.0)
≥75 to <85	33 (34.4)
≥85	9 (9.3)
Male, n (%)	81 (84.4)
Female, n (%)	15 (15.6)
Race, n (%)	
White	64 (66.7)
Asian	26 (27.1)
Missing	6 (6.3)
ECOG PS, n (%)	
0	70 (72.9)
1	26 (27.1)

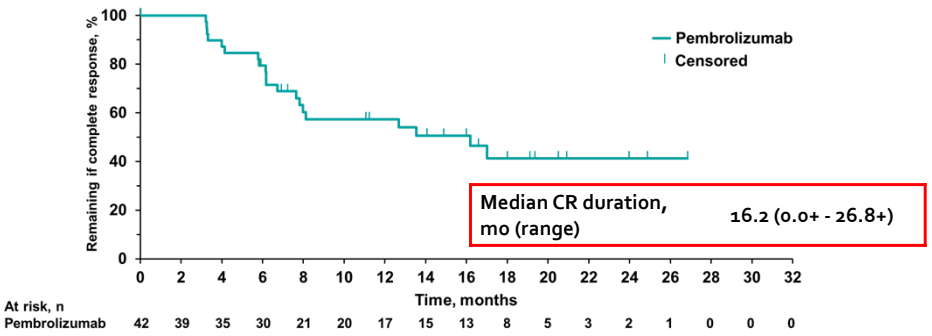
Characteristic	N=97
Median prior BCG instillations, n (range)	12.0 (7.0-45.0)
Tumor pattern at study entry, n (%)	
CIS with T1	12 (12.5)
CIS with high-grade Ta	24 (25.0)
CIS alone	60 (62.5)
PD-L1 status, n (%)	
CPS ≥10	35 (36.5)
CPS <10	56 (58.3)
Not evaluable	5 (5.2)
Reason prior cystectomy not performed, n (%)	
Declined	91 (94.8)
Ineligible	5 (5.2)

FDA ODAC, 2019

KEYNOTE-057:

BCG Unresponsive CIS Patients Achieving CR with Pembrolizumab

Best response	N=96 n (%)	95% CI
CR	39 (40.2)	31.5, 51.4



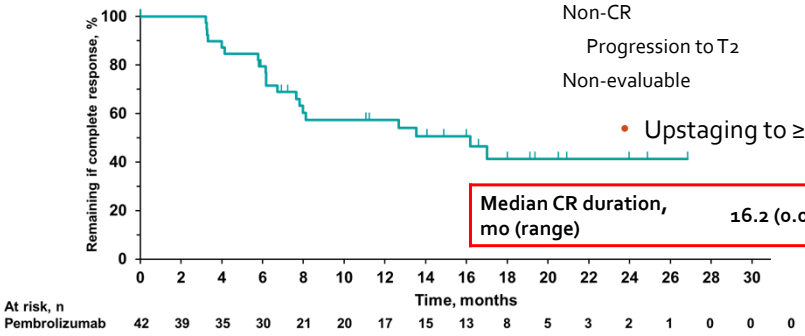
CR, complete response. [a]1 month = 30.4367 days. [b]Month 0 = time point when initial CR was achieved.
Database cutoff: February 20, 2019.

FDA ODAC, 2019

KEYNOTE-057:

BCG Unresponsive CIS Patients Achieving CR with Pembrolizumab

Best response	N=96 n (%)	95% CI
CR	39 (40.6)	30.7, 51.1
Non-CR	56 (58.3)	47.8, 68.3
Progression to T2	0	NA, NA
Non-evaluable	1 (1.0)	0, 5.7



- Upstaging to ≥ pT2 in 8.3% patients

Median CR duration, mo (range) **16.2 (0.0+ - 26.8+)**

CR, complete response. [a]1 month = 30.4367 days. [b]Month 0 = time point when initial CR was achieved.
Database cutoff: February 20, 2019.

FDA ODAC, 2019

Immune-mediated AEs of Any Grade and Corresponding Grade 3 or 4[a] Events

Incidence of any-grade immune-mediated AEs, n (%)	N=102
Any	21 (20.6)
Hypothyroidism	8 (7.8)
Hyperthyroidism	5 (4.9)
Pneumonitis	3 (2.9)
Hypophysitis	1 (1.0)
Colitis	1 (1.0)
Adrenal insufficiency	1 (1.0)
Nephritis	1 (1.0)
Severe skin reaction	1 (1.0)
Type 1 diabetes mellitus	1 (1.0)
Uveitis	1 (1.0)
Hepatitis	1 (1.0)

Incidence of grades 3 or 4 immune-mediated AEs, n (%)	N=102
Any	3 (2.9)
Hypothyroidism	0 (0.0)
Hyperthyroidism	0 (0.0)
Pneumonitis	0 (0.0)
Hypophysitis	0 (0.0)
Colitis	0 (0.0)
Adrenal insufficiency	1 (1.0)
Nephritis	0 (0.0)
Severe skin reaction	1 (1.0)
Type 1 diabetes mellitus	1 (1.0)
Uveitis	0 (0.0)
Hepatitis	0 (0.0)

Balar AV, et al. *EMUC*. 2019

New FDA Approval in NMIBC

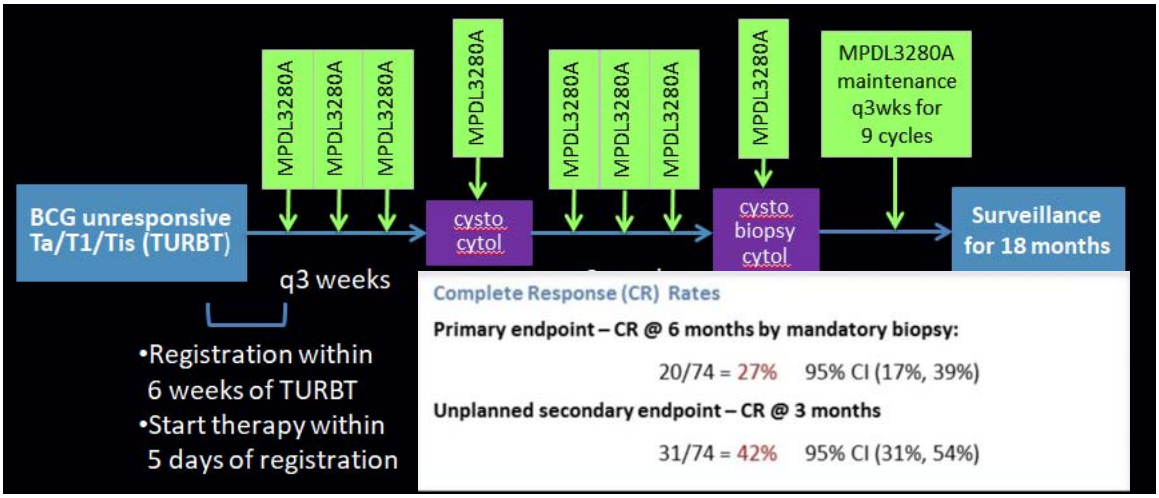
FDA APPROVED

January 8, 2020

Pembrolizumab is approved for the treatment of patients with BCG-unresponsive, high-risk, NMIBC with carcinoma in situ (CIS) with or without papillary tumors who are ineligible for, or who have elected not to undergo, cystectomy

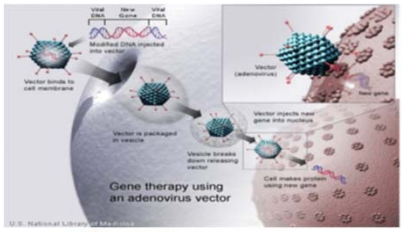
FDA Prescribing Information.

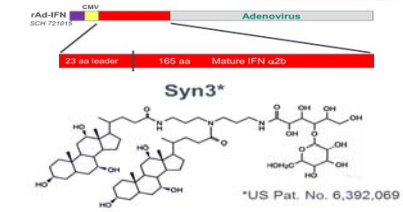
SWOG-S1605: Atezolizumab (MPDL3280A) in BCG Unresponsive High Risk NMIBC



PI: Black, Singh: ASCO 2020

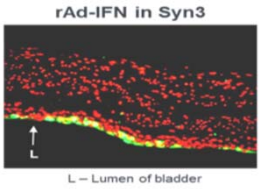
Adstiladrin™ (nadofaragene firadenovec)



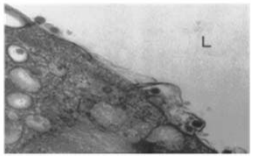


Syn3*

*US Pat. No. 6,392,069



Adenovirus particles on bladder epithelium and within vesicles using Syn3



Protein active in transfected cells

Released into microenvironment

Ferring Pharmaceuticals

F/K/D

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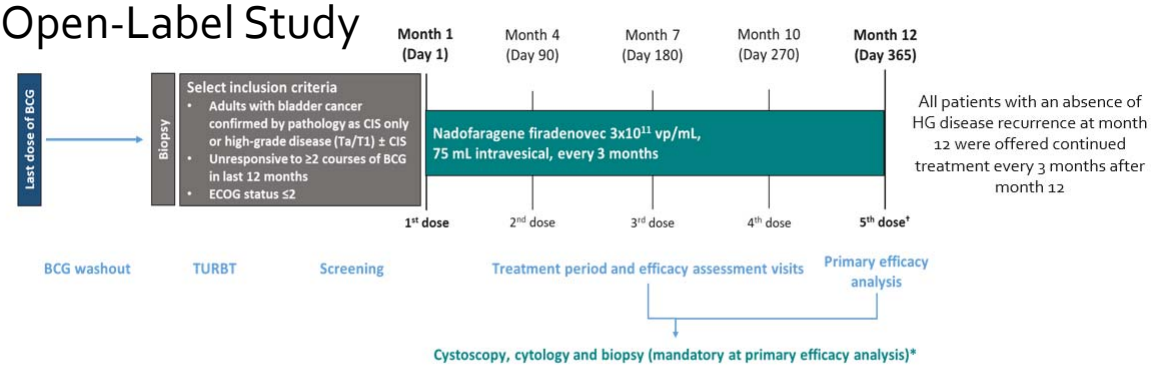
Nadofaragene Firadenovec: Phase 3, Multi-Center, Open-Label Study



All patients with an absence of HG disease recurrence at month 12 were offered continued treatment every 3 months after month 12

- **Primary Endpoint:** To evaluate the CR rate in patients with CIS (with or woithout HG Ta or T1 papillary disease) at any time after the first installation of rAd-IFNα/Syn3
- **Secondary objectives:** To evaluate the durability of the CR in patients with CIS with/without concomitant HG Ta or T1 papillary disease and To evaluate the rate and durability of HG-RFS in patients with HG Ta or T1 papillary disease only

Boorjan SA, et al. ASCO GU. 2020; Shore N, et al. EAU20 Virtual, July 18

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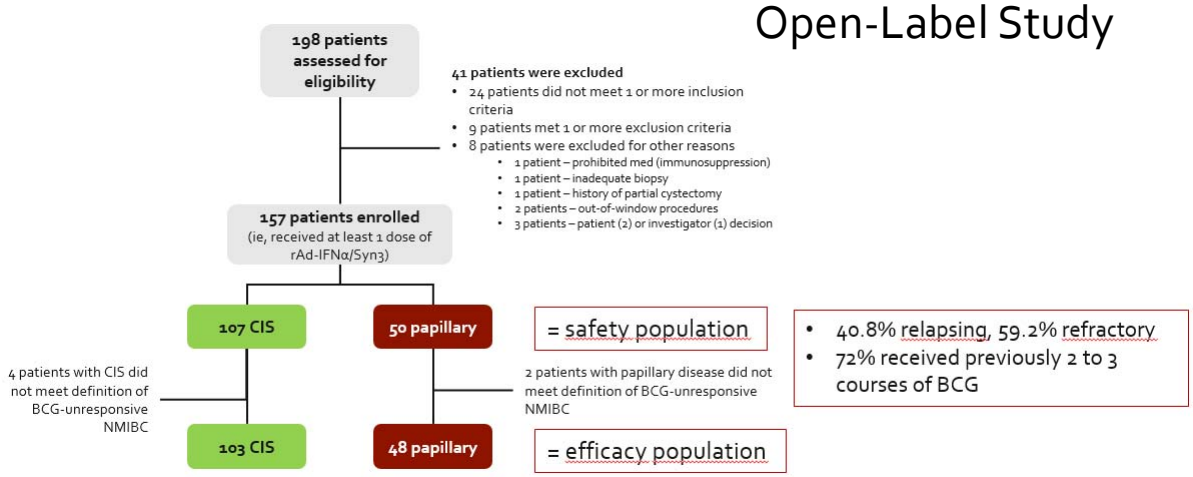
Nadofaragene Firadenovec: Phase 3, Multi-Center, Open-Label Study



Boorjan SA, et al. ASCO GU. 2020; Shore N, et al. EAU20 Virtual, July 18

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Nadofaragene Firadenovec: Phase 3, Multi-Center, Open-Label Study

Patients achieving HGRF survival (n, %)	CIS +/- Ta/T1 (N=103)	Papillary Disease (N=48)	Total (N=151)
3 mos	55 (53.4)	35 (72.9)	90 (59.6)
6 mos	42 (40.8)	30 (62.5)	72 (47.7)
9 mos	36 (35.0)	28 (58.3)	64 (42.4)
12 mos	25 (24.3)	21 (43.8)	46 (30.5)

Median duration of HG-RFS was 12.35 months (95% CI: 6.67, NE) in patients with papillary disease
Progression to ≥ MIBC in 8 (5.3%) patients

Boorjan SA, et al. ASCO GU. 2020; Shore N, et al. EAU20 Virtual, July 18

Nadofaragene Firadenovec: Phase 3, Multi-Center, Open-Label Study

The most common TEAEs were

- instillation site discharge (33.1%),
- fatigue (23.6%),
- bladder spasm (19.7%),
- micturition urgency (17.8%), and
- hematuria (16.6%)

% of Patients		Total, n = 157
Any	Any TEAE	93.0
	Serious TEAE	8.9
	Grade 3	17.2
	Grade 4	1.3
	Grade 5	0
Drug related	Any TEAE	70.1
	Serious TEAE	0.6
	Grade 3	3.8
	Grade 4/5	0
Discontinuation of study drug	Any TEAE	1.9
	Drug-related TEAE	1.9

Boorjan SA, et al. ASCO GU. 2020; Shore N, et al. EAU20 Virtual, July 18

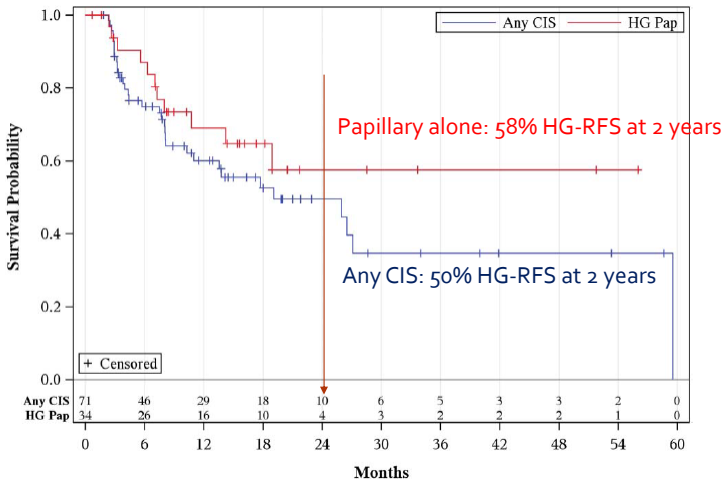
Multi-Institution Evaluation of Sequential Gemcitabine and Docetaxel as Rescue Therapy for Nonmuscle Invasive Bladder Cancer

Ryan L. Steinberg, Lewis J. Thomas, Nathan Brooks, Sarah L. Mott, Andrew Vitale, Trafford Crump, Mounica Y. Rao, Marcus J. Daniels, Jonathan Wang, Supriya Nagaraju, William C. DeWolf, Donald L. Lamm, Max Kates, M. Eric Hyndman, Ashish M. Kamat,* Trinity J. Bivalacqua, Kenneth G. Nepple and Michael A. O'Donnell†,‡

- 276 patients
  - median age 73 years, median follow up 22.9 months
- HG RFS: 65% and 52%, at 1 and 2 yr
  - RFS: 60% and 46%, at 1 and 2 yr
- 15.6% went on to cystectomy (median 11.3 months from induction)
  - 4.0% had progression to muscle invasion.

Steinberg, Kamat, O'Donnell et al, J Urol, May 2020

High grade bladder recurrence-free survival for BCG unresponsive cases



40% patients reported AEs but only 9.4% had schedule impacted and only 3.3% were unable to tolerate full induction course

Steinberg, Kamat, O'Donnell et al, J Urol, May 2020

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Table 1. *Side effects of gemcitabine/docetaxel intravesical therapy*

	No. (%)
Overall	
Any side effects:	
No	164 (59.4)
Yes	112 (40.6)
Treatment schedule affected by side effect:	
No	248 (90.6)
Yes	26 (9.4)
Missing	2
Specific side effects	
Dysuria:	
No	233 (84.4)
Yes	43 (15.6)
Hematuria:	
No	247 (89.5)
Yes	29 (10.5)
Urinary frequency/urgency:	
No	215 (77.9)
Yes	61 (22.1)
Urinary retention:	
No	272 (98.6)
Yes	4 (1.4)

Steinberg, Kamat, O'Donnell et al, J Urol, May 2020

Summary

- Radical Cystectomy is the recommended treatment for patients who have high grade recurrence after adequate BCG therapy
- Most patients would like to try alternative therapies
- Alternatives include:
  - Pembrolizumab (approved Jan 2020)
  - Gem/Docetaxel combination
  - Nadofaragene firadenovec
  - Vicinium

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Management of NMIBC:

Practical Solutions for Common Problems

Summer School Webinar Series
July 30, 2020

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DISCLOSURES

NONE

The Ohio State University
Wexner Medical Center

CASE PRESENTATION

- 67 year old very active male with a history of hypertension, hyperlipidemia and prior cigarette use for many years evaluated for gross hematuria. He has stable LUTS characterized by mostly storage symptoms. Prior appendectomy.
- CT urogram unremarkable other than small filling defects in the bladder suggestive of clot
- Urine cytology: Suspicious for malignancy
- Office cystoscopy: Multiple papillary tumors

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OPERATIVE EVALUATION

EUA: Prostate moderately enlarged with no palpable abnormalities and mobile bladder without a palpable mass or induration

Cystoscopy/TURBT:

Normal urethra with lateral lobe enlargement

8 papillary tumors in the bladder located near the trigone, posterior wall and right lateral wall. Size ranged from 1-3cm.

Complete visual TURBT and 3 specimens submitted to pathology

QUESTIONS

- Is there a benefit of adding **HAL-assisted (Cysview®) blue light cystoscopy** at the time of TURBT for this patient?

- How do you decide when to complement TURBT with HAL-assisted blue light cystoscopy?

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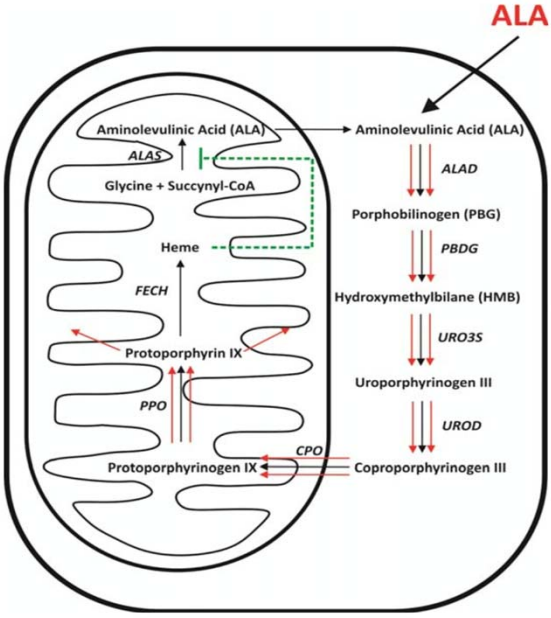
Fluorescence-Based Photodynamic Diagnosis (PDD)
Blue Light Cystoscopy



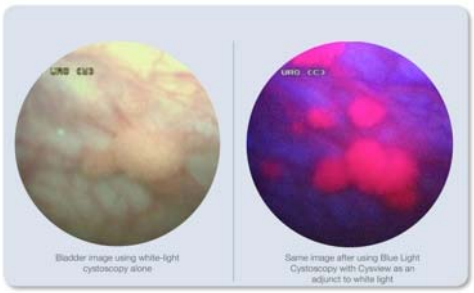
ALA is a naturally occurring compound
In heme biosynthesis pathway

Heme biosynthesis pathway utilizes mitochondria and cytoplasm

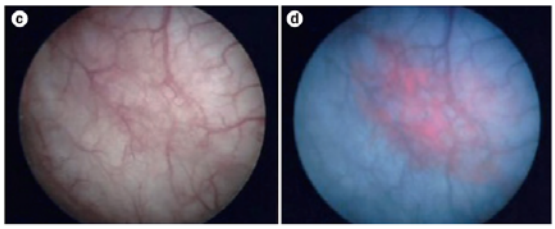
Protoporhyrin IX is photosensitizing

Cancer cells enzymatic machinery results
In preferential accumulation of protoporphyrin IX relative to normal cells

Illumination with blue light (380-450 nm); protoporphyrin IX emits red flurorescence



Do These Images Benefit My Patients?



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American Urological Association

Guideline Statements (Diagnosis)

30. **<u>Enhanced Cystoscopy</u>**: In a patient with NMIBC, a clinician should offer **blue light cystoscopy** at the time of TURBT, if available, to increase detection and decrease recurrence. (Moderate Recommendation; Evidence Strength: Grade B)

Chang, et al. JUrol 196 (4):1021–1029, 2016

THE OHIO STATE UNIVERSITY
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CASE PRESENTATION
PATHOLOGY RESULT

Specimen 1 (Trigone):
High grade Ta urothelial cancer with CIS
Muscularis propria present and uninvolved

Specimen 2 (Posterior wall):
High grade Ta urothelial cancer with CIS
Muscularis propria present and uninvolved

Specimen 3 (Right lateral wall):
High grade Ta urothelial cancer
No lamina propria invasion
No muscularis propria identified

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QUESTIONS

- Would you recommend a **repeat TURBT** in this patient?

- Other than T1 bladder cancer or visually incomplete first TURBT for NMIBC when do you recommend repeat TURBT?

The Ohio State University
Wexner Medical Center

Guideline Statements: Restaging TURBT

Guideline Statement	Clinical Context	Strength of Rec
Variant Histology (7)	Pursuing bladder preservation in a patient with variant histology	Expert Opinion
TURBT/ Restaging Resection (12)	Incomplete initial resection : re-TURBT of all remaining tumor if technically feasible	Grade B
TURBT/ Restaging Resection (13)	High-risk, high-grade Ta tumors: consider repeat transurethral resection	Grade C
TURBT/ Restaging Resection (14)	T1 disease: perform repeat TUR of the primary tumor site to include muscularis propria	Grade B

CASE PRESENTATION
MANAGEMENT

- Completed **full dose induction BCG** with limited local toxicities
- **First follow up cystoscopy subtle areas of redness** adjacent to areas of recent TURBT and urine **cytology suspicious for malignant cells**

QUESTION

- Does the patient need an **OR evaluation** of the **abnormal endoscopic and/or cytology findings?**

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CASE PRESENTATION
MANAGEMENT

- OR evaluation was performed and limited to cup biopsy and fulguration of the areas of erythema (white light ONLY).

Pathology: CIS

- Continued on maintenance BCG and experienced increased local toxicities with doses 2 and 3 that he found very bothersome

Next follow up cystoscopy (~6 months) was normal and urine cytology was normal

QUESTIONS

- What was the **likelihood that persistent CIS** following induction BCG would **respond to additional maintenance BCG** at the 6 month evaluation?
- Was the disease state best characterized as BCG unresponsive after completing induction BCG? Has he **received** what is considered **adequate BCG**?

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How Often Do BCG Toxicities Occur?

63% local symptoms of frequency, urgency, dysuria
31% systemic symptoms of malaise, fever, joint aches
23% episode of gross hematuria
23% culture proven bacterial cystitis
0.3% BCG sepsis

EORTC study of full dose versus 1/3 dose and 1 year versus 3 year maintenance BCG: Eur Urol 2014

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Additional Points About BCG

- Side effect profile does not become worse with increasing number of doses
  (i.e. comparing induction to first, second and third year of maintenance)
  (Eur Urol, 2014)
- Discontinuation rate is low (7.8%) and most often event occurs during first year (2/3 of patients who eventually discontinue do so within the first year)
  (Eur Urol, 2014)
- **However in any given patient with toxicity must consider reducing dose or alternate week therapy AFTER trying single dose fluoroquinolone administered 4-6 hours after treatment**

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CASE PRESENTATION
MANAGEMENT

- Continued on maintenance BCG
- Next follow up **cystoscopy (~9 months) two small papillary tumors** and urine cytology reported as normal
- TURBT: two 1 cm papillary tumors on the posterior wall of the bladder. No other abnormal findings. (white light ONLY)
- **Pathology: Multifocal high grade Ta urothelial cancer**. Muscularis propria identified and not involved

QUESTIONS

- At the time of the TURBT would you have performed **prostatic urothelial biopsies? Random bladder biopsies?**
- Now that he has recurrent papillary high grade Ta disease at 9 months **how is the disease best characterized?**
  - BCG early relapsing
  - BCG late relapsing
  - BCG unresponsive
  - BCG refractory
- **What are his treatment options?**

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CASE PRESENTATION
MANAGEMENT

- Continued on maintenance BCG
- **Follow up cystoscopy (~12 months) was normal but urine cytology reported as suspicious for malignant cells.**
- CT urogram was normal and referred to a tertiary medical center
- OR evaluation included HAL-assisted blue light cystoscopy. Several fluorescing flat lesions in the bladder. TUR biopsies of the prostate were performed. No further upper urinary tract evaluation was performed.
- **Pathology: CIS of the bladder**

QUESTIONS

- Is this BCG unresponsive disease?
- Treatment Options:
  - -Radical Cystectomy
  - -Pembrolizumab
  - -Therapies currently under FDA review
  - -Clinical Trial
  - -**Let's focus on intravesical chemotherapy**
    - Valrubicin **X**
    - **Gemcitabine**
    - **Mitomycin C**
    - **Gemcitabine/Docetaxol**

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THANK YOU FOR JOINING US TODAY!

Q&A