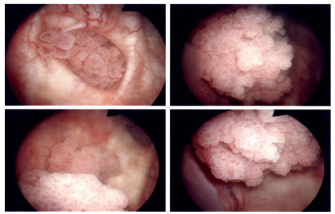
Updates and Controversies in NMIBC



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Risk Stratification in NMIBC

AUA/SUO Guidelines: Risk Stratification

- At the time of each occurrence/recurrence, a clinician should assign a clinical stage and classify a patient accordingly as low-, intermediate, or high-risk

AUA/SUO Risk Stratification

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

European Association of Urology

Table 6.3: Risk group stratification

Risk group stratification	Characteristics
Low-risk tumours	Primary, solitary, Ta, G1* (PUNLMP, LG), < 3 cm, no CIS
Intermediate-risk tumours	All tumours not defined in the two adjacent categories (between the category of low- and high-risk).
High-risk tumours	Any of the following: • T1 tumour • G3** (HG) tumour • CIS • Multiple and recurrent and large (> 3 cm) Ta, G1G2 tumours (all conditions must be presented in this point)*

Babjuk, M, et al. 2017 Eur Urol 71(3) 447

European Association of Urology

Platinum Priority – Review – Urothelial Cancer

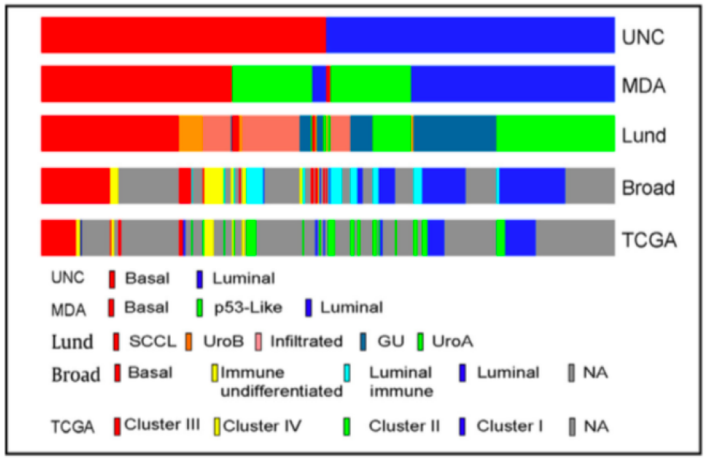
Genetic Alterations in the Molecular Subtypes of Bladder Cancer: Illustration in the Cancer Genome Atlas Dataset

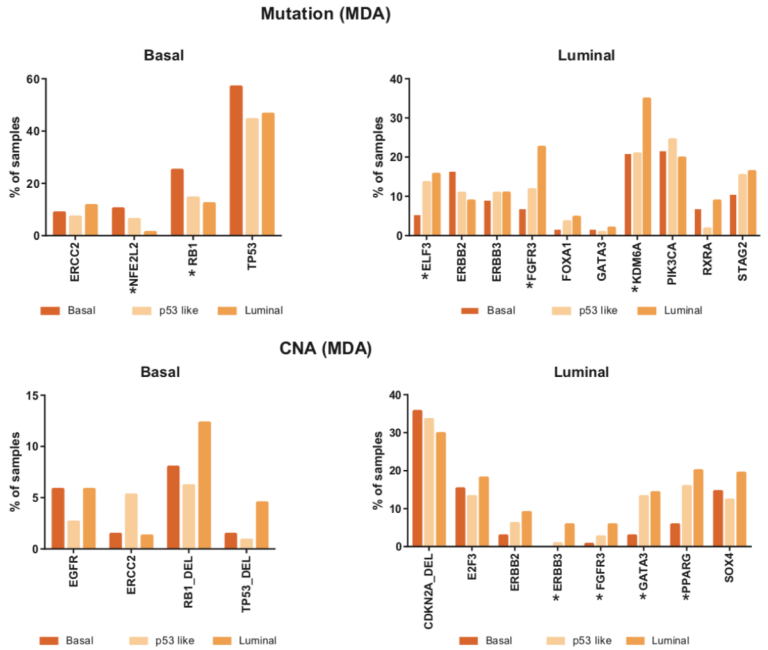
Woonyoung Choi [a,b], *Andrea Ochoa* [a,b], *David J. McConkey* [a,b,*], *Mattias Aine* [c], *Mattias Höglund* [c], *William Y. Kim* [d], *Francisco X. Real* [e,f], *Anne E. Kiltie* [g], *Ian Milsom* [h], *Lars Dyrskjøt* [i], *Seth P. Lerner* [j]

"The molecular subtypes in other solid tumors are enriched with specific mutations and copy number aberrations that are thought to underlie their distinct progression patterns, and biological and clinical properties."

Choi W, Ochoa A, McConkey DJ, et al: European Urology 2017: 1–12

Is this the future of risk stratification?





"Luminal tumors contain more alterations in FGFR3 and KDM6A (also known as UTX) genes that are more commonly mutated in NMIBCs.."

"Basal/SCC-like MIBCs frequently contain RB1 mutations, a property that they share with basal-like breast cancers…"

Choi W, Ochoa A, McConkey DJ, et al: European Urology 2017: 1–12

Risk Stratification in NMIBC

- Do you use it?
- Which classification do you use?
- If so, how?
- What does the future look like?

How does variant histology alter your management?

Guidelines: Variant Histology

- An experienced GU pathologist should review pathology with regards to variant or suspected variant histology
- (micropapillary, nested, plasmacytoid, neuroendocrine, squamous or glandular differentiation)

  (Moderate Recommendation; Evidence Strength: Grade C)

- If a bladder sparing is considered with variant histology, then a restaging TURBT within four to six weeks of the initial TURBT

  (Expert Opinion)

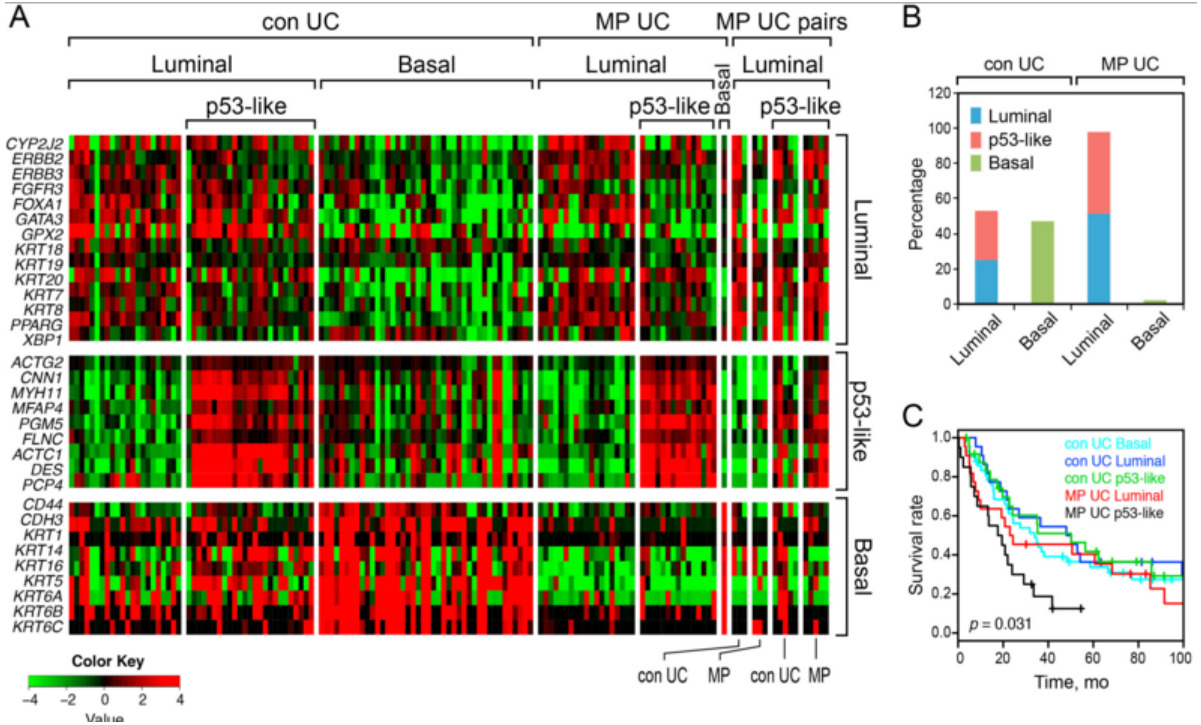
- Due to the high rate of upstaging associated with variant histology, consider initial radical cystectomy. (Expert Opinion)

Why Variants Matter

- Many retrospective studies suggests that variant histology portends worse outcomes
- Higher propensity of locally advanced disease
  - Greater degree of lymph node metastasis
- Upstaging at radical cystectomy: HR 2.77
- Different responses to therapy – BCG, chemotherapy or radiotherapy

Wasco et al, J Urol, 2007; Domanowska, Human Pathology, 2007; Turker et al, BJUI, 2012; Kassouf, Urology, 2009; Willis, J Urol, 2014

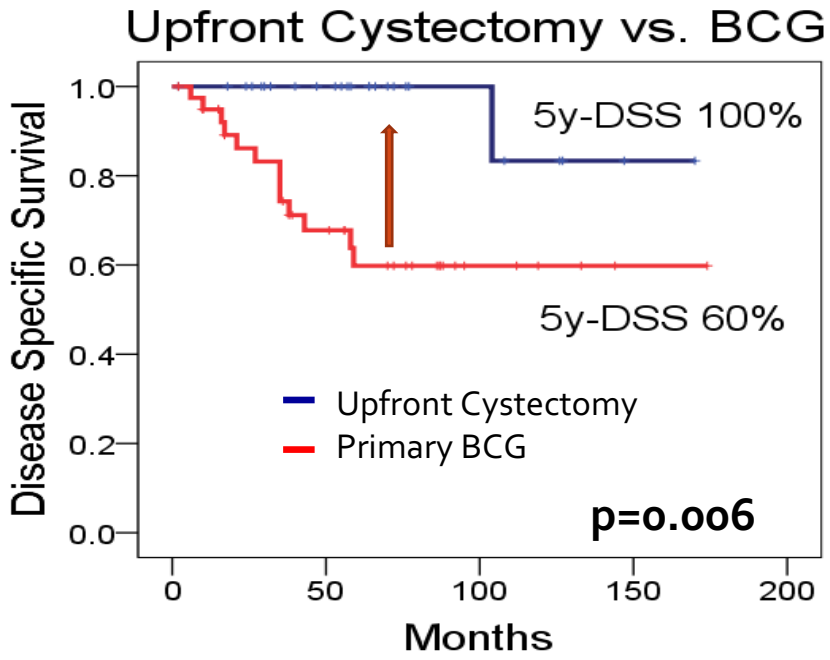
Micropapillary Bladder Cancer clusters with Luminal Type Urothelial Carcinoma



Gao CC et al, Eur Urol, 2016

Early Radical Cystectomy Associated with Improved Disease-specific Survival

Upfront Cystectomy (n=36) versus Primary BCG (n=40)



Willis, … Kamat et al, J Urol, 2015

MSKCC Series with MP Variant

- N = 36; FU: 3 years
- All negative on reTUR
- 5-year DSS
  - BCG: 75% vs 83% with cystectomy, p = 0.8
- Metastatic rate at 5 years
  - BCG: 34% vs 21% with cystectomy, p = 0.9
- Authors concluded: Conservative mgt with BCG “acceptable”

Spaliviero M & Herr HW et al. J Urol 2014 192(3):702

Variant Histology

- What is the role of second opinion pathology
- How does variant histology impact your management?
  - Micropapillary variant
  - Plasmacytoid
  - Nested variant

Perioperative Chemotherapy

Guidelines: Single Instillation therapy

- With low or intermediate risk, consider a single post-op instillation of IVe chemotherapy (e.g., mitomycin C) within 24 hours of TURBT

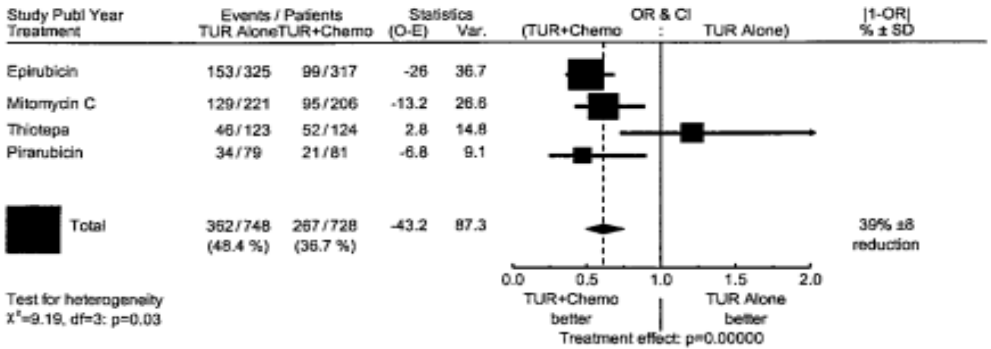


FIG. 2. Forest plot of recurrence by treatment

Sylvester 2004

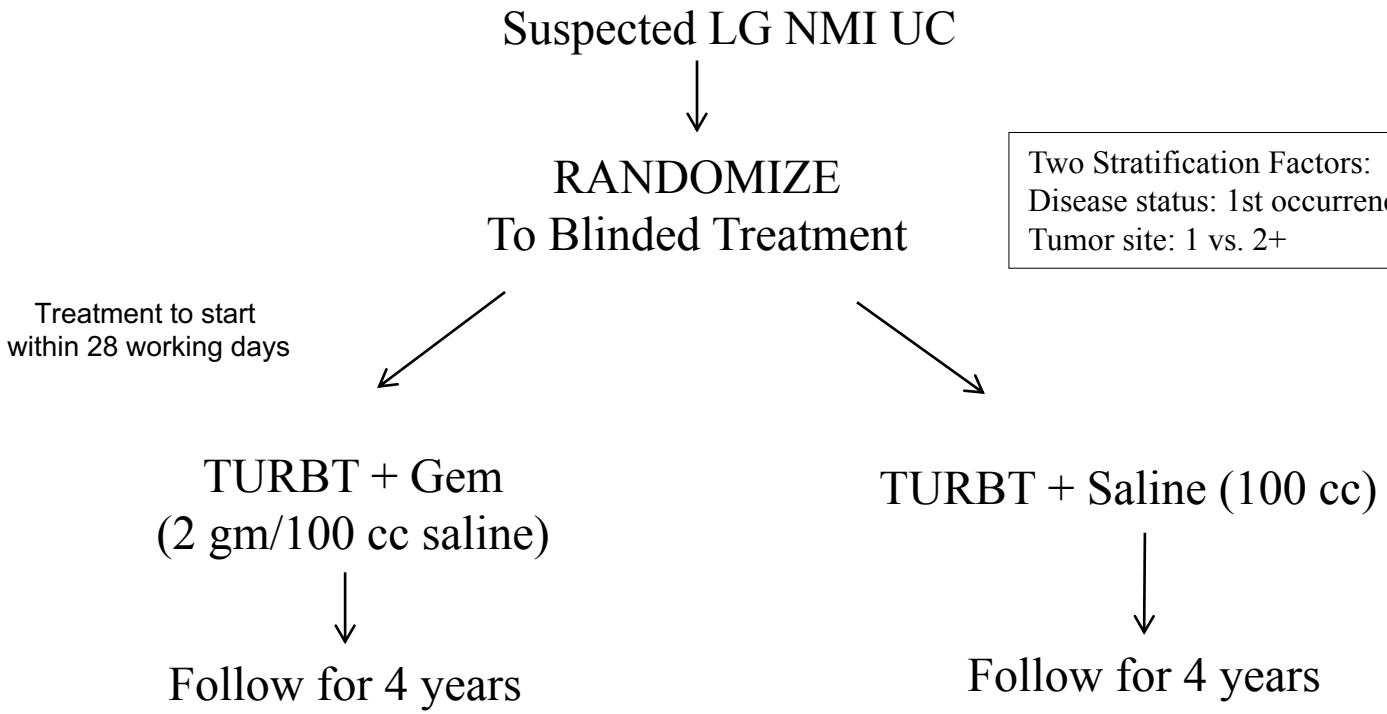
New Data: SWOG S0337

A Phase III Blinded Study of Immediate Post-TURBT Instillation of Gemcitabine Versus Saline in Patients with Newly Diagnosed or Occasionally Recurring Grade I/II Superficial Bladder Cancer

- 345 patients
- Gemcitabine (2 grams/100cc of saline) vs. saline
- Dwell time: 60 minutes
- Side effect profiles: no differences
- Only 62% had correct pathology (low grade disease), noting the inaccurate cystoscopy assessment by urologists of tumor grade

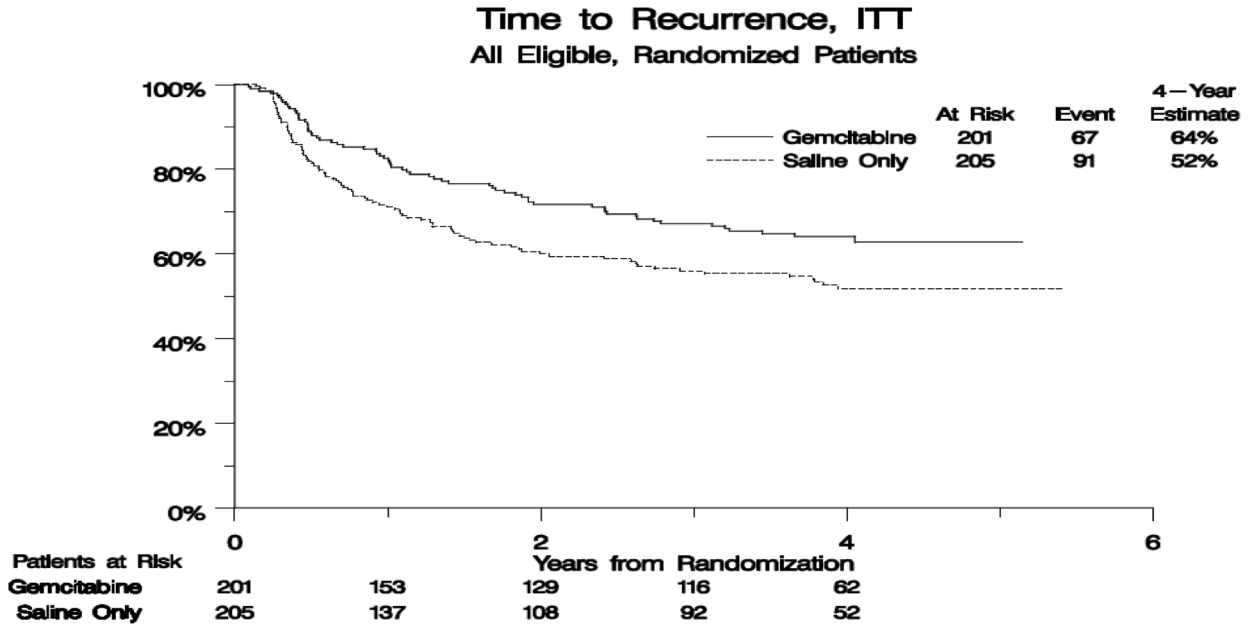
Messing EM, et al. JAMA. 2018;319(18):1880

S0337 Schema



Messing EM, et al. JAMA. 2018;319(18):1880

S0337 Results



Messing EM, et al. JAMA. 2018;319(18):1880

SWOG S0337 – Summary

- Gemcitabine reduces recurrence of LG NMI UC by 47%
  - HR = 0.53 (95% CIs 0.35 – 0.81) (p = 0.003)
    (54% [S] → 34% [G])
- Safe, well tolerated, readily available
- No adverse outcomes for HG NMI UC
- Is this the new standard for suspected LG NMI UC?

- Comment on Cost:
  - Gemcitabine significantly more cost effective than Mitomycin-C
  - $36.90 vs. $1068.00

Messing EM, et al. JAMA. 2018;319(18):1880

Do you use perioperative chemotherapy

- If so, what % of appropriate patients?
- If so, which agent/s do you use?

Do You Use Enhanced Imaging?

Guidelines: Enhanced Cystoscopy

- In a patient with NMIBC, you should offer Blue Light cystoscopy at the time of TURBT, if available, to increase detection and decrease recurrence

  (Moderate Recommendation; Evidence Strength: Grade B)

- In a patient with NMIBC, you should consider use of NBI to increase detection and decrease recurrence

  (Conditional Recommendation; Evidence Strength: Grade C)

Detection and Recurrence with NBI

- Results indicated that NBI increased NMIBC detection by 9.9% at the per-patient and 18.6% at the per-lesion

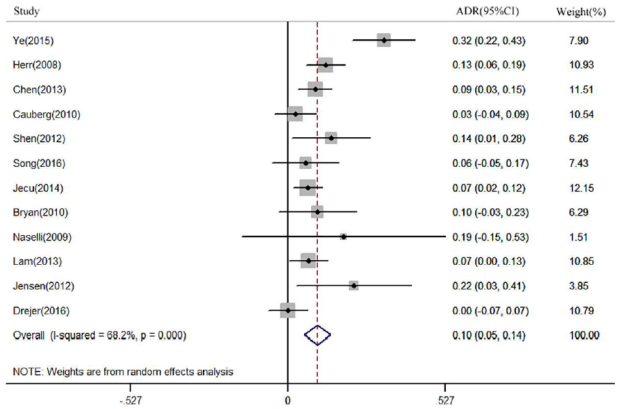


Fig 2. Forest plot of the pooled additional detection rate (ADR) of Narrow-band imaging (NBI) when compared to White light cystoscopy (WLC) for non-muscle invasive bladder cancer (NMIBC) detection in per-patient analysis.

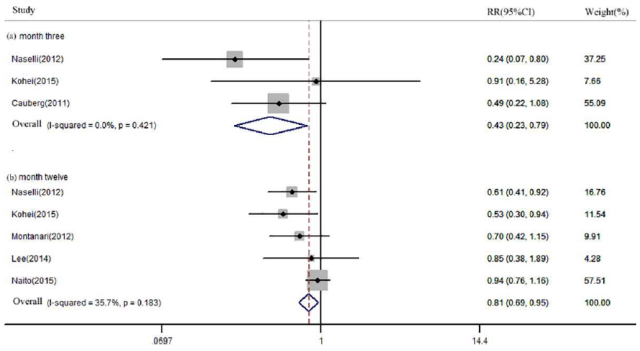


Fig 5. Forest plot of the pooled relative risk (RR) for Narrow-band imaging (NBI) compared to White light cystoscopy (WLC) at month three (a) and twelve (b).

Xiong Y. et al. PLoS One. 2017; 12(2): e0170819

Blue Light: Impact on Detection

Detection of additional tumors in patients with at least one Ta or T1 tumor an additional carcinoma in situ (CIS) lesions in patients with at least one CIS lesion

Tumor Type	Patients in who at least one Ta or T1 tumor was detected only by BL, n (%)	Meta-Analysis Event Rate	Patients in whom at least one CIS lesion was detected only by BL, n (%)	Meta-Analysis Event Rate
Total	188/831 (22.6%)	24.9%; p < 0.001 (0.184-0.328)	68/268 (25.4%)	26.7%; p< 0.001 (0.183-0.371)
Primary cancer	66/360 (18.3%)	20.7%; p < 0.001 (0.131-0.312)	31/111 (27.9%)	28.0%; p< 0.001 (0.193-0.388)
Recurrent cancer	122/471 (25.9%)	27.7%; p < 0.001 (0.218-0.343)	37/157 (23.6%)	25.0%; p< 0.001 (0.168-0.354)
High risk	97/397 (24.4%)	27.0%; p < 0.001 (0.168-0.402)	-	-
Intermediate risk	84/350 (33.6%)	35.7%; p = 0.004 (0.271-0.453)	-	-
Low risk	7/183 (3.8%)	5.4%; p < 0.001 (0.026-0.106)	-	-

At least one additional Ta/T1 was found in 24.9% of the patients (p<0.001), along with, 26.7% of the CIS patients were diagnosed with BLC with Cysview only p<0.001

19. Burger et al: European Journal of Urology 2013

Blue Light: Impact on Recurrence

	Patients treated with BL, n (%)	Patients treated with WL, n (%)	Total	Follow-up period
Herman et al.	27/68 (39.7%)	38/77 (49.4%)	145	12 months
Stenzl et al.	72/200 (36.0%)	92/202 (45.5%)	402	9 months
Dragoescu et al.	8/42 (19.0%)	17/45 (37/8%)	87	12 months
Total	107/310 (34.5%)	147/324 (45.4%)	634*	p=0.006; RR=0.761 (0.627-0.924)
At least on T1 or CIS	26/74 (35.1%)	48/87 (51.7%)	161*	p=0.052; RR=0.696 (0.482-1.003)
At least one Ta			524*	p=0.040; RR=0.804 (0.653-0.991)
High- risk subgroup	46/126 (36.5%)	70/144 (48.6%)		p=0.05; RR=0.752 (0.565-1.000)
Inter.-risk subgroup	43/95 (45/3%)	40/74 (54/1%)		p=0.246; RR=0.836 (0.617-1.132)
Low-risk subgroup	14/78 (17.9%)	34/98 (34.7%)		p=0.029; RR=0.561 (0.334-0.944)

Rate of recurrence is reduced by 10.9% p= <0.006

Burger et al: European Journal of Urology 2013
Grossman et al: Journal of Urology 2012

Efficacy and Safety of Blue Light Flexible Cystoscopy with Hexaminolevulinate in the Surveillance of Bladder Cancer: A Phase III, Comparative, Multicenter Study

Siamak Daneshmand,* Sanjay Patel, Yair Lotan,† Kamal Pohar, Edouard Trabulsi, Michael Woods, Tracy Downs, William Huang, Jeffrey Jones, Michael O'Donnell, Trinity Bivalacqua,† Joel DeCastro, Gary Steinberg,‡ Ashish Kamat, Matthew Resnick, Badrinath Konety, Mark Schoenberg, J. Stephen Jones and Flexible Blue Light Study Group Collaborators

From the University of Southern California (SD), Los Angeles, California, University of Oklahoma (SP), Oklahoma City, Oklahoma, University of Texas Southwestern Medical Center (YL), Dallas and Veterans Affairs Medical Center (JJ) and University of Texas M. D. Anderson Cancer Center (AK), Houston, Texas, Ohio State University (KP), Columbus and Cleveland Clinic (JSJ), Cleveland, Ohio, Sidney Kimmel Medical College at Thomas Jefferson University (ET), Philadelphia, Pennsylvania, University of North Carolina (MW), Chapel Hill, North Carolina, University of Wisconsin (TD), Madison, Wisconsin, New York University School of Medicine (WH) and Columbia University Medical Center (JD), New York and Montefiore Medical Center (MS), Bronx, New York, University of Iowa (MO), Iowa City, Iowa, Johns Hopkins University (TB), Baltimore, Maryland, University of Chicago (GS), Chicago, Illinois, Vanderbilt University (MR), Nashville, Tennessee, and University of Minnesota (BK), Minneapolis, Minnesota

Daneshmand S, Patel S, Lotan Y, et al: J Urol 2018; 199: 1158–1165

Proportion of Patients Where Recurrence* Detected Only With BLFCC

Proportion of Patients where Recurrence was Detected only with BLFCC	Result/Statistic[1]
Patients with recurrence	63
Patients with recurrence seen only with BL[2]	13
Proportion	**20.6%**
95% CI	(11.5%, 32.7%)
P value[3]	**<.0001**

Detection of patients with recurrence was significantly improved using BLFCC

Daneshmand S, Patel S, Lotan Y, et al: J Urol 2018; 199: 1158–1165

Proportion of Patients Where CIS Detected Only with BLCC in OR Examination

Proportion of Patients where CIS was Detected only with BLCC	
	Result/Statistic[1]
Patients with confirmed CIS	26
Patients with CIS seen only with BL[2]	9
Proportion	**34.6%**
95% CI	(17.2%, 55.7%)
P value[3]	<.0001

41% of patients with recurrence recurred with CIS

Daneshmand S, Patel S, Lotan Y, et al: J Urol 2018; 199: 1158–1165

Do you use enhanced imaging?

- If so, for whom?
- If so, which technology and why?
- Do you think office based blue light will be practical?

Future Directions

- What will Risk Stratification look like?
- Will molecular staging trump histology?
- Will single shot gemcitabine be the new standard?
- Will enhanced technology (Blue Light) become the office standard?