Difficult Issues in Non-Muscle Invasive Bladder Cancer: Guidelines and Beyond

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“Good judgment comes from experience, and a lot of that comes from bad judgment.”

Purpose of 2016 AUA Guidelines

The survival rate for the majority of patients with non-muscle invasive bladder cancer (NMIBC) is favorable; however, the rates of **recurrence and progression** to muscle-invasive bladder cancer (MIBC) are major determinants of long-term outcome.

The recurrence and progression **probability rates depend on several clinical and pathologic factors**. Therefore, the ability to predict risk of recurrence and progression and treat the disease appropriately is important. This guideline **provides a risk-stratified clinical framework for the management of NMIBC.**

Guidelines: Diagnosis

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

2. **At initial diagnosis, a complete resection of the bladder tumor(s), when technically feasible, should be done. (Clinical Principle)**

Incomplete TURBT is likely a significant contributing factor to early bladder cancer recurrences, as **tumors are seen at first surveillance cystoscopy in up to 45% of patients**

Brausi 2002

Guidelines: Diagnosis

3. **A clinician should perform upper urinary tract imaging as a component of the initial evaluation** of a patient with bladder cancer. **(Clinical Principle)**

4. **In a patient with a history of NMIBC with normal cystoscopy and positive cytology, consider prostatic urethral biopsies and upper tract imaging, as well as enhanced cystoscopic techniques (blue light when available), ureteroscopy, or random bladder biopsies. (Expert Opinion)**

Guidelines: Risk Stratification

5. **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." (Moderate Recommendation; Evidence Strength: Grade C)**

- **EORTC/CUETO Model → Tumor size, number, grade, stage, recurrence pattern, number**

- **AUA/SUO Additions → Lymphovascular invasion, prostatic urethral involvement, variant histology, poor response to BCG**

AUA/SUO Risk Stratification Table

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

Guidelines: Variant Histology

6. **An experienced GU pathologist should review the pathology when in doubt with regards to variant or suspected variant histology. (e.g., micropapillary, nested, plasmacytoid, neuroendocrine, sarcomatoid), extensive squamous or glandular differentiation, or the presence/absence of lymphovascular invasion. (Moderate Recommendation; Evidence Strength: Grade C)**

7. **If a bladder sparing approach is being considered in a patient with variant histology, then a restaging TURBT within four to six weeks of the initial TURBT. (Expert Opinion)**

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

Guidelines: Urine Markers

9. In surveillance of NMIBC, a clinician should not use urinary biomarkers in place of cystoscopic evaluation. (Strong Recommendation; Evidence Strength: Grade B)

Direct comparisons between markers are difficult, and given the uncertainty in sensitivity, these tests cannot be use to replace cystoscopy.

NMP22®	Protein-based; identifies nuclear matrix protein involved in the mitotic apparatus
BTA®	Protein-based; identifies a basement membrane antigen related to complement factor H
UroVysion® FISH	Cell-based; identifies altered copy numbers of specific chromosomes using fluorescent probes
ImmunoCyt™	Cell-based; identifies three cell surface glycoproteins
Cxbladder™	Cell-based; identifies the presence of five mRNA fragments

Tomasini 2013; O'Sullivan 2012

Guidelines: Urine Markers

10. In a patient with a history of low-risk cancer and a normal cystoscopy, a clinician should not routinely use a urinary biomarker or cytology during surveillance. (Expert Opinion)

11. In a patient with NMIBC, a clinician may use biomarkers to assess response to BCG (UroVysion® FISH) and adjudicate equivocal cytology (UroVysion® FISH and ImmunoCyt™). (Expert Opinion)

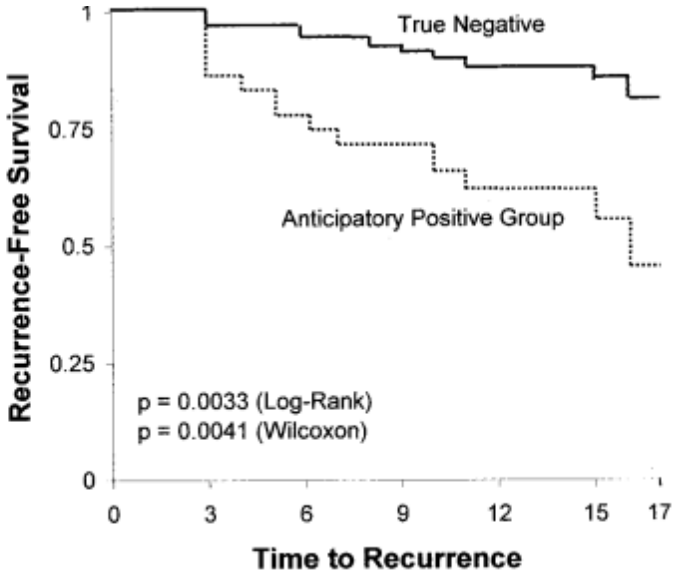


FIG. 3. Time to recurrence is significantly less (p = 0.014) for anticipatory positive cases (negative cystoscopy, positive FISH) versus negative cystoscopy, negative FISH cases.

Sarosdy 2002

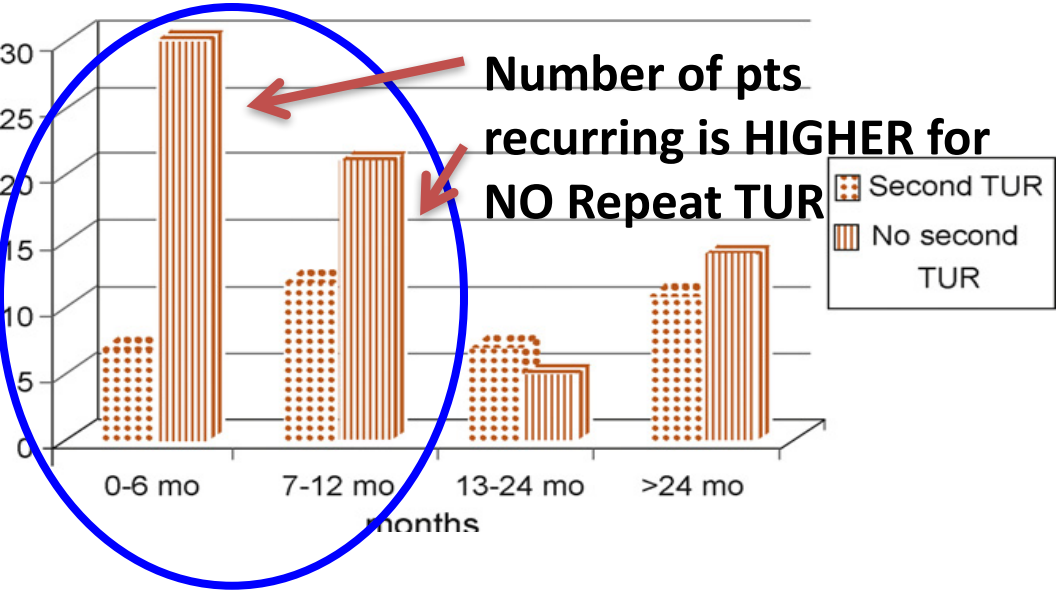
Guidelines: **Repeat TURBT**

12. **In a patient with NMIBC who underwent an incomplete initial resection (not all visible tumor treated), a repeat TUR of all remaining tumor should be done if technically feasible. (Strong Recommendation; Evidence Strength: Grade B)**

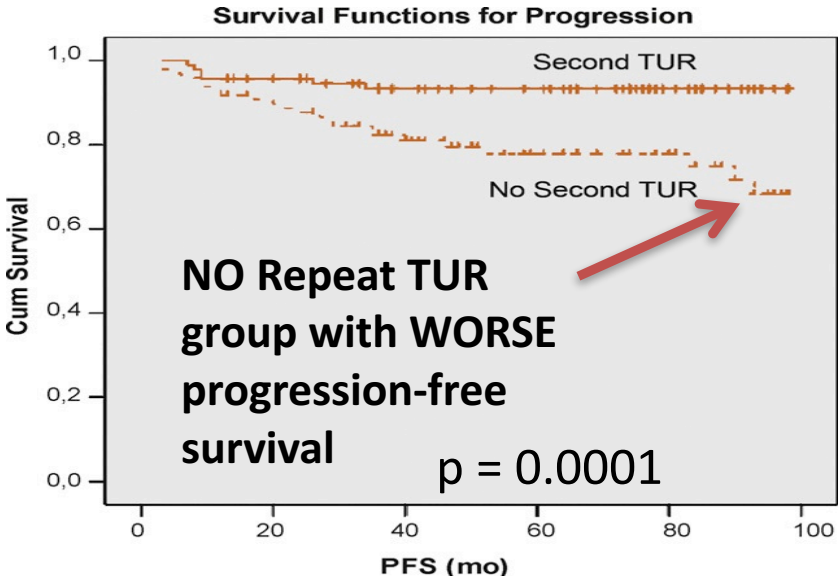
13. **In a patient with high-risk, high-grade Ta tumors, consider performing repeat TUR of the primary tumor site within six weeks of the initial TURBT. (Moderate Recommendation; Evidence Strength: Grade C)**

14. **In a patient with T1 disease, should perform repeat TUR of the primary tumor site to include muscularis propria within six weeks of the initial TURBT. (Strong Recommendation; Evidence Strength: Grade B)**

Repeat TURBT in T1 Tumors: RCT



Number of pts recurring is HIGHER for NO Repeat TUR



Randomized T1 cohort of 210 patients

Divrik, et al Eur Urol 58:185, 2010

So Who Should Undergo Repeat TUR?

- Incomplete resection of tumor
  - pertains to any low or high grade NMIBC
- Should consider with *any* high grade Ta
- Must with bladder conservation in any T1
- Must with bladder conservation in any variant histology

Guidelines: **Single Shot** Intravesical Therapy

15. In a patient with suspected or known low- or intermediate-risk NMIBC should consider administration of a single postoperative instillation of intravesical chemotherapy (e.g., mitomycin C or epirubicin) within 24 hours of TURBT. In case of a suspected perforation or extensive resection, you should NOT use postoperative chemotherapy. (Moderate Recommendation; Evidence Strength: Grade B)

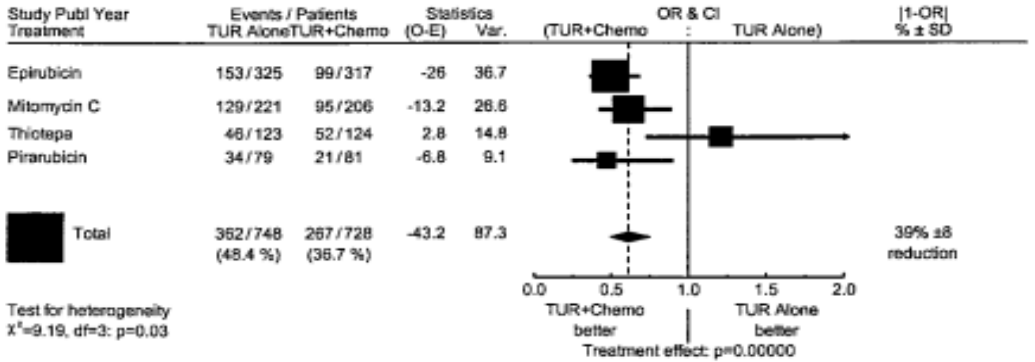


FIG. 2. Forest plot of recurrence by treatment

Sylvester 2004

Guidelines: **Induction** Intravesical Therapy

16. **In a low-risk patient, you should NOT administer induction intravesical therapy. (Moderate Recommendation; Strength of Evidence Grade C)**

17. **In an intermediate-risk patient, you should consider administration of a six week course of induction intravesical chemotherapy *or* BCG. (Moderate Recommendation; Evidence Strength: Grade B)**

18. **In a high-risk patient with newly diagnosed CIS, high-grade T1, or high-risk Ta UCC, you should administer a six-week induction course of BCG. (Strong Recommendation; Evidence Strength: Grade B)**

Guidelines: BCG

There is insufficient evidence to recommend one strain of BCG

- Several small studies suggest that different strains may have different efficacies

There is insufficient evidence to prescribe a particular BCG strength

- EORTC 30962 recommends full dose for three years for high-risk patients
- For lower-risk patients, no difference in recurrence free survival between full or 1/3 dose at 1 or 3 years

There is insufficient evidence to recommend using BCG in combination with other intravesical agents (AT THIS TIME…)

- Several ongoing trials are currently examining synergistic combinations

Rentsch 2014; Oddens 2013; Houghton 2013

Guidelines: **Maintenance** Intravesical Therapy

19. **In an intermediate-risk patient who completely responds to an induction course of intravesical chemotherapy, a clinician may utilize maintenance therapy. (Conditional Recommendation; Evidence Strength: Grade C)**

20. **In an intermediate-risk patient who completely responds to induction BCG, you should consider maintenance BCG for one year, as tolerated. (Moderate Recommendation; Evidence Strength: Grade C)**

21. **In a high-risk patient who completely responds to induction BCG, you should continue maintenance BCG for three years, as tolerated. (Moderate Recommendation; Evidence Strength: Grade B)**

Guidelines: BCG Relapse and Salvage Tx

22. **In an intermediate- or high-risk patient with persistent or recurrent disease or positive cytology following intravesical therapy, you should consider performing prostatic urethral biopsy and an upper tract evaluation prior to additional intravesical therapy. (Conditional Recommendation; Evidence Strength: Grade C)**

23. **In an intermediate- or high-risk patient with persistent or recurrent Ta or CIS disease after a single course of induction intravesical BCG, a clinician should offer a second course of BCG. (Moderate Recommendation; Strength of Evidence C)**

24. **In a patient fit for surgery with high-grade T1 disease after a single course of induction intravesical BCG, a clinician should offer radical cystectomy. (Moderate Recommendation; Evidence Strength: Grade C)**

Guidelines: BCG Relapse and Salvage Tx

25. A clinician should not prescribe additional BCG to a patient who is intolerant of BCG or has documented recurrence on TURBT of high-grade, NMIBC and/or CIS within six months of two induction courses of BCG or induction BCG plus maintenance. (Moderate Recommendation; Evidence Strength: Grade C)

26. In a patient with persistent or recurrent intermediate- or high-risk NMIBC who is unwilling or unfit for cystectomy following two courses of BCG, you may recommend clinical trial. A clinician may offer this patient intravesical chemotherapy when clinical trials are unavailable. (Expert Opinion)

Guidelines: Cystectomy

27. **In a patient with Ta low- or intermediate-risk disease, you should not perform radical cystectomy until bladder-sparing modalities (staged TURBT, intravesical therapies) have failed. (Clinical Principle)**

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 histology, you should consider initial radical cystectomy. (Moderate Recommendation; Evidence Strength: Grade C)**

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, you should offer radical cystectomy. (Moderate Recommendation; Evidence Strength: Grade C)**

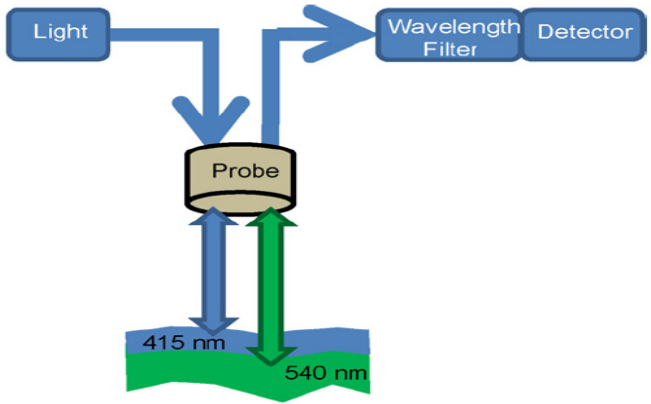
Guidelines: Enhanced Cystoscopy

30. **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)**

31. **In a patient with NMIBC, you may consider use of NBI to increase detection and decrease recurrence (Conditional Recommendation; Evidence Strength: Grade C)**

Narrow Band Imaging

- Tissues illuminated with light of narrow bandwidth
- Centered on blue (415 nm) and green (540 nm) spectrum
- Strongly absorbed by Hgb thus highlighting vascular structures



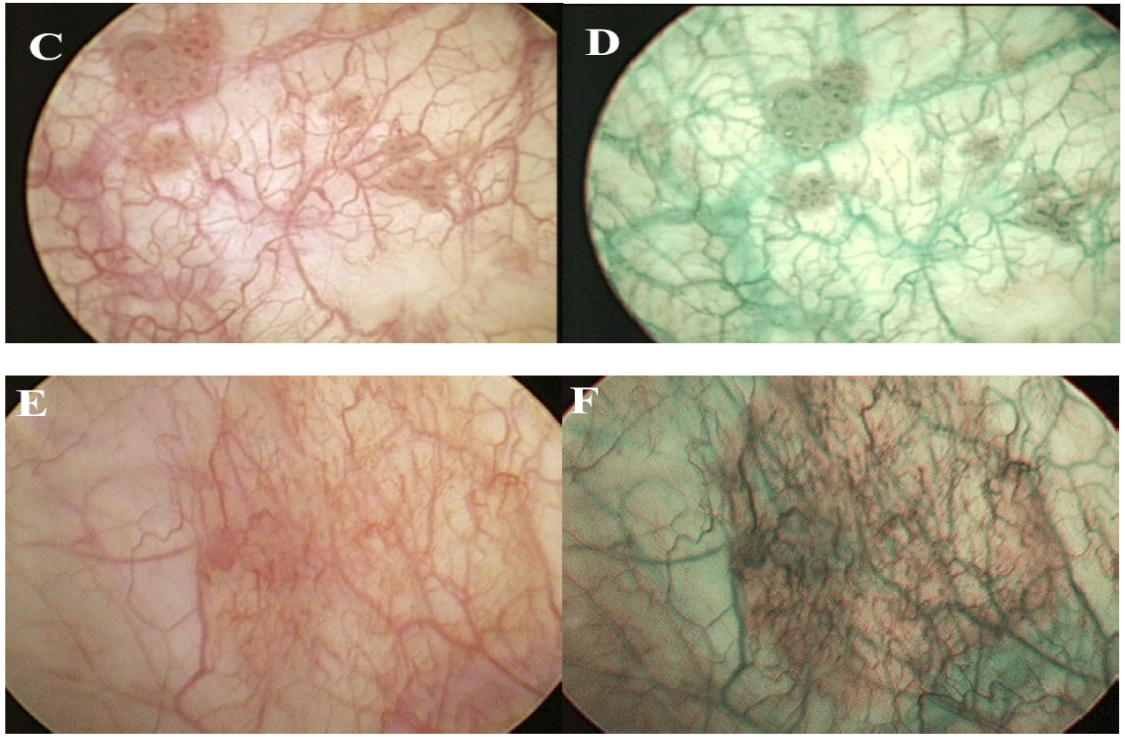
Cauberg ECC et al. Eur Urol 56: 287, 2009

Narrow Band Imaging

- Capillaries/small vessels on surface = brown
- Veins in submucosa = cyan
  - Greenish blue color
  - “Like water of shallow beach”

Cauberg ECC et al. Eur Urol 56: 287, 2009

Narrow Band Imaging™ (NBI)



Cauberg EC et al. Urol 76: 658, 2010

- Olympus Optical imaging technology enhances visibility of vessels on mucosa.
- Filters the white light into specific light wavelengths that penetrate only surface of human tissue and are absorbed by hemoglobin.
- Bluish light enhances **superficial capillary network (brown)**
- Greenish light enhances **deeper vessel visibility: vessels are greenish-blue (cyan)**

Narrow Band Imaging (NBI)

A Randomized Prospective Trial to Assess the Impact of Transurethral Resection in Narrow Band Imaging Modality on Non–Muscle-Invasive Bladder Cancer Recurrence

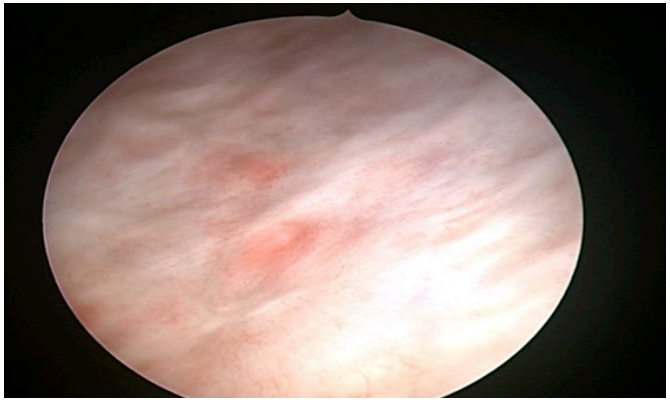
Angelo Naselli [a,], Carlo Introini [a], Luca Timossi [a], Bruno Spina [b], Vincenzo Fontana [c], Riccardo Pezzi [c], Francesco Germinale [d], Franco Bertolotto [d], Paolo Puppo [a,d]*

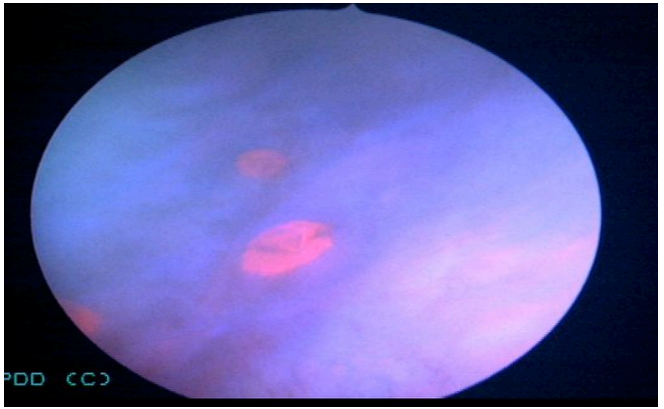
- **148 pts NMIBC randomized to NBI-TUR vs. WL-TUR**

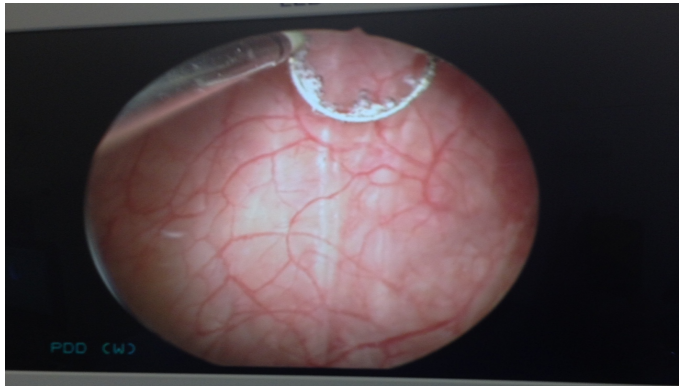
	White Light	NBI	p value
Detection	1.36 lesions/patient	1.55 lesions/patient	0.07
3 mo recurrence	16.7%	3.9%	0.008
1 year recurrence	51.4%	31.6%	0.014

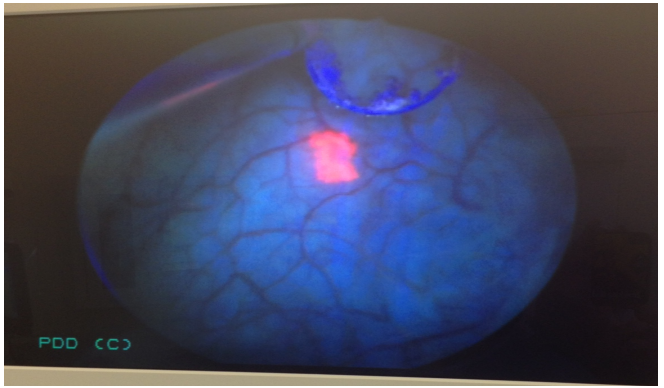
Naselli A et al. Eur Urol 61: 908, 2012

Cysview™ (Blue Light Cystoscopy)







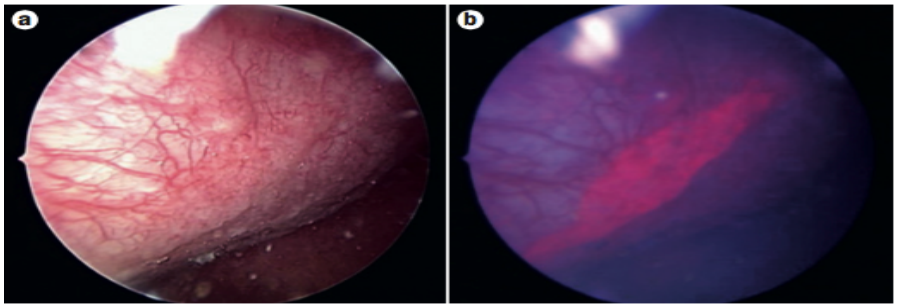


Blue Light Cystoscopy with Cysview

- Hexaminolevulinic acid was approved in Europe in 2005 under the name Hexvix
- Hexvix became FDA approved in the United States in 2010 as Cysview with the Karl Storz Photodynamic system
- Cysview is manafactured by Photocure, a Norweigian pharmaceutical company

How Blue Light Works

- After instillation, Hexvix bypasses cellular regulation mechanisms for heme synthesis
- Leads to selective accumulation of Protoporphyrin IX (PpIX) in neoplastic cells due to increased mitotic rate
- Levels up to 10 times greater in tumors than in normal tissue



Mark Jr et al,. The Canadian Journal of Urology. 2012;19(2):6227-6231.
"MOA - Cysview." *Cysview MOA Comments*. N.p., n.d. Web. 26 Aug. 2015.

5 Different Trials: Cysview Detected Significantly More Ta, T1 and CIS **tumors** than white light

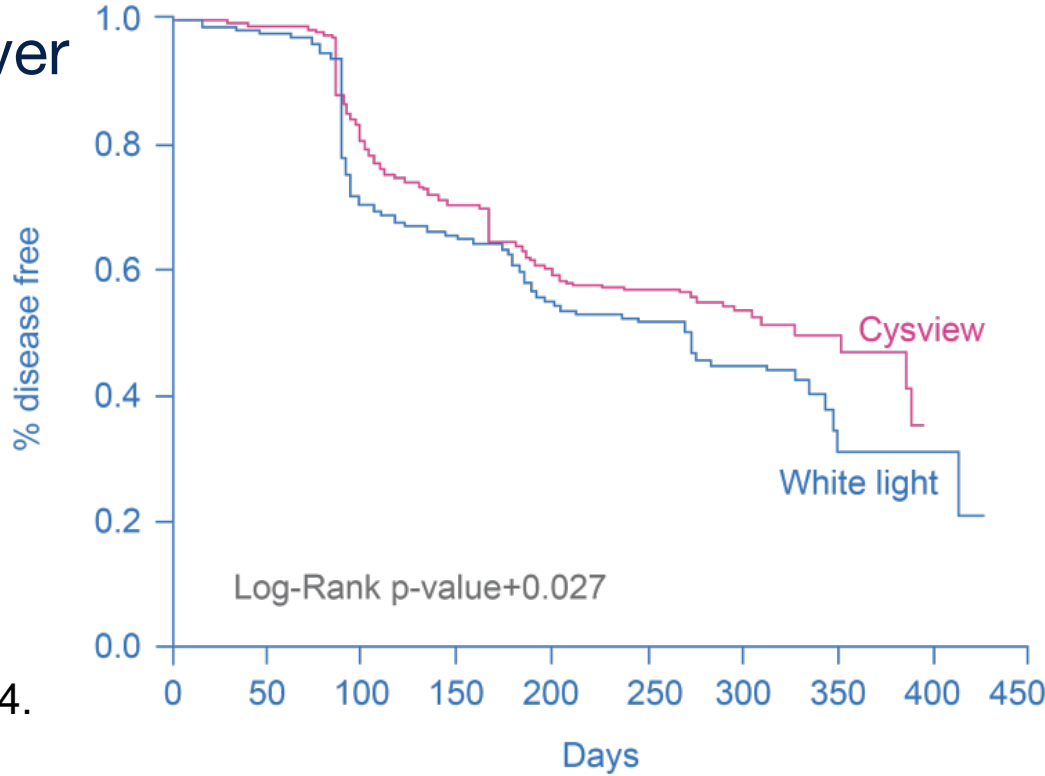
Tumour type	Both methods, n (%)	Cysview only, n (%)	RR (CI) in favor of Cysview	P value
Total Ta	1247 (81.6%)	202 (13.2%)	2.136 (1.578-2.890)	<0.001
Ta initial	477 (88.7%)	49 (9.1%)	3.992 (1.833-7.040)	<0.001
Ta recurrent	770 (77.7%)	153 (15.4%)	1.970 (1.399-2.775)	<0.001
High risk	440 (80.0%)	73 (13.3%)	1.867 (1.186-2.939)	0.007
Intermediate risk	649 (80.7%)	123 (15.3%)	3.132 (1.992-4.926)	<0.001
Low risk	158 (90.3%)	6 (3.4%)	0.702 (0.244-2.021)	0.512
Total T1	308 (85.3%)	34 (9.4%)	1.807 (0.957-3.412)	0.068
Initial	200 (85.8%)	26 (11.2%)	3.978 (1.617-9.785)	0.003
Recurrent	108 (84.4%)	8 (6.3%)	0.689 (0.247-1.922)	0.477
Total CIS	281 (55.1%)	203 (39.8%)	10.949 (6.808-17.610)	<0.001
Initial	119 (55.3%)	91 (42.3%)	20.651 (7.766-54.909)	<0.001
Recurrent	162 (54.9%)	112 (38.0%)	7.581 (4.364-13.168)	<0.001

Witjes JA, et al. Eur Urol. 2014

U.S. Pivotal Study – Recurrence Results

- Tumor recurrence rates over 9 months were
  - 47% with Cysview
  - 56% with white light (p=0.026)

- Relative reduction in recurrence rate was 16%



1.Stenzl A *et al. J Urol* 2010; **184**: 1907-1914.
2.Burger M *et al.* EAU 2012.

Guidelines: Surveillance & Follow-up

32. **After completion of the initial evaluation and treatment, you should perform the first surveillance cystoscopy within three to four months. (Expert Opinion)**

33. **For a low-risk patient whose first surveillance cystoscopy is negative for tumor, you should perform subsequent surveillance cystoscopy six to nine months later, and then annually thereafter; surveillance after five years in the absence of recurrence should be based on shared-decision making between the patient and clinician. (Moderate Recommendation; Evidence Strength: Grade C)**

34. **In an asymptomatic patient with a history of low-risk NMIBC, you should not perform routine surveillance upper tract imaging. (Expert Opinion)**

35. **In a patient with a history of low-grade Ta disease and a noted sub-centimeter papillary tumor(s), you may consider in-office fulguration as an alternative to resection under anesthesia. (Expert Opinion)**

Guidelines: Surveillance and Follow-up

35. For an intermediate-risk patient whose first surveillance cystoscopy is negative for tumor, you should perform subsequent cystoscopy with cytology every 3-6 months for 2 years, then 6-12 months for years 3 and 4, and annually thereafter. (Expert Opinion)

36. For a high-risk patient whose first surveillance cystoscopy is negative for tumor, you should perform subsequent cystoscopy with cytology every three to four months for two years, then six months for years three and four, and then annually thereafter. (Expert Opinion)

37. For an intermediate- or high-risk patient, you should consider performing surveillance upper tract imaging at one to two year intervals. (Expert Opinion)

Even if you are on the right track, you'll get run over if you just sit there."

Will R

Future Research

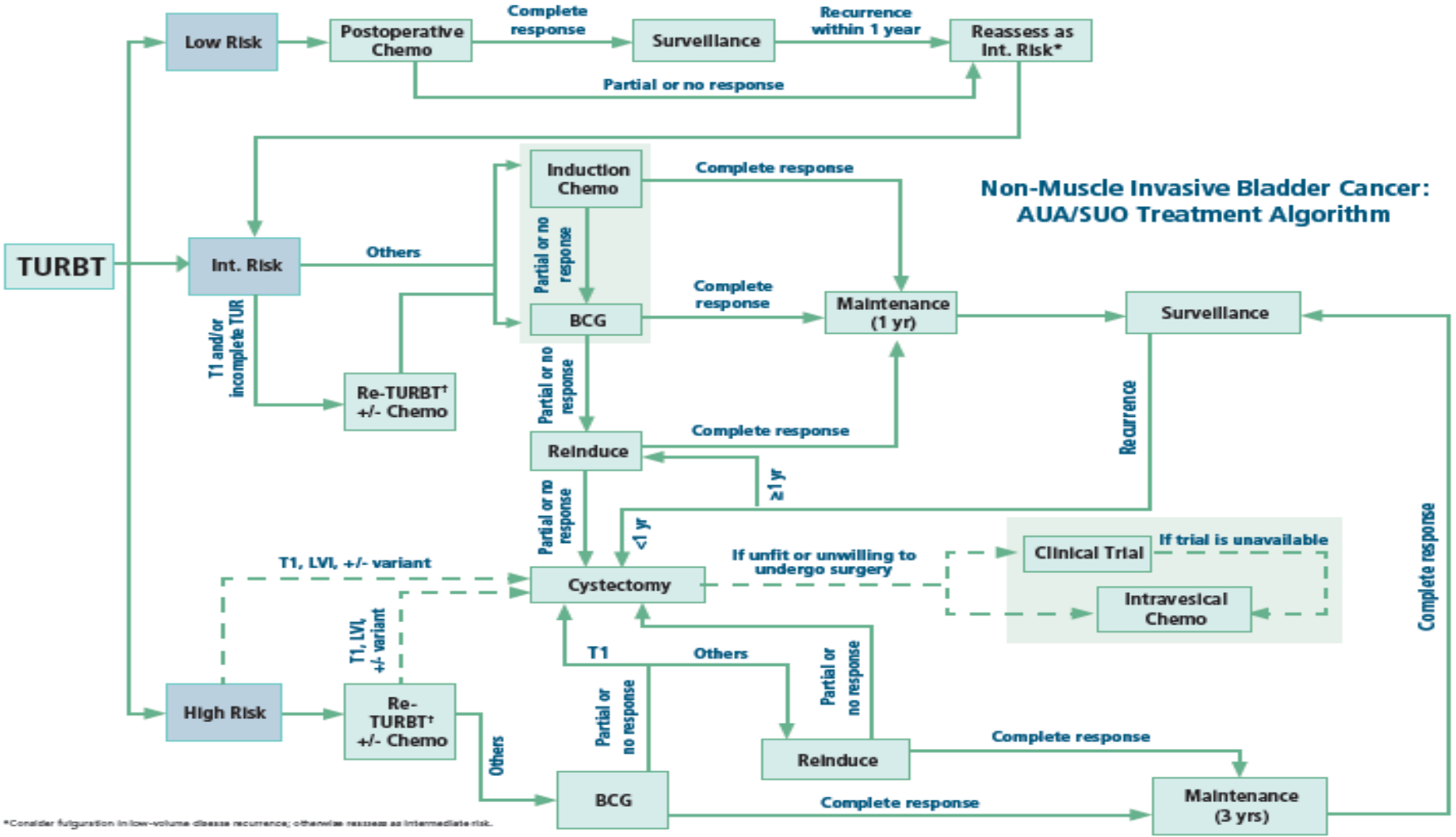
The future of NMIBC will likely be driven forward by science, novel technologies, new therapeutics and clinical trials.

- *Bladder Cancer Genome Atlas Project*
- *Novel agents to improve BCG efficacy or manage BCG failures*
- *New technologies*
  - A Study of Blue Light Flexible Cystoscopy With Cysview in the Detection of Bladder Cancer in the Surveillance Setting-- NCT02560584
  - Transurethral Resection of Bladder Tumors Using PK Button Vaporization Electrode or Monopolar Loop Electrocautery in Treating Patients with Bladder Cancer-- NCT01567462
- *Surveillance*
  - Surveillance Guidelines in Monitoring Patients with Non-muscle Invasive Bladder Cancer-- NCT02298998

Take Home Points

- Risk Stratification
- Value of repeat TUR
  - Incomplete TUR, high grade Ta, any T1, variants
- Judicious Use of Technology
  - Blue light, NBI
- Use of Maintenance BCG
  - 1-year for intermediate risk
  - 3-years for high risk
- Identification of BCG Failure
  - Role of Radical Cystectomy in select HR NMIBC

Non-Muscle Invasive Bladder Cancer: AUA/SUO Treatment Algorithm



*Consider fulguration in low-volume disease recurrence; otherwise reassess as intermediate risk.

†Ideally re-TURBT within six weeks. Should be performed if there was muscle resection on incomplete resection, and/or if bladder cancer treatment (e.g., intravesical therapy or surveillance) is being planned.

Acknowledgments

Non-muscle Invasive Bladder Cancer Panel

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