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Urothelial Carcinoma

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Outline

- **NMIBC**
  - Risk adapted strategy
  - AUA guidelines
- **Muscle invasive bladder cancer**
  - AUA Guidelines
  - Perioperative chemotherapy
  - Perioperative management
  - Bladder sparing protocols

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* Bladder Cancer Incidence and Prevalence

Incidence

- Over 79,000 new cases each year in the US (NIH 2016)
- > 16,000 deaths/year e each year in US (NIH 2016)

Prevalence

- In 2012, there were an estimated 577,403 people living with bladder cancer in the United States.

Who Dies From This Cancer?

- Bladder cancer is the ninth leading cause of cancer death in the United States.
- 4.4 deaths per 100,000 men and women per year based on 2008-2012 deaths.
- The percent of bladder cancer deaths is highest among people aged 75-84.
- **Median Age At Death: 79**

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Ref: SEER Stats: Cancer of the Urinary Bladder 2015
www.seer.cancer.gov

Risk Factors

- Smoking
- Cyclophosphamide
- Schistosomiasis (SCC)
- Chronic catheter (SCC)
- Lynch Syndrome
- Pelvic radiation
- **Occupations (exposure)**
  - Industrial/Chemical Exposure
  - Fire Fighter
  - Rubber of textile workers
  - Truck or Taxi driver
  - Hairdresser
  - Miners
  - Aristocholic acid

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Other Factors

- Age (Median Age is 73)
- Sex (75:25 Male : Female)
- Race (41% of all UC patients presenting are Caucasian)
- Chronic Bladder Inflammation

Daneshmand. Etiology and epidemiology of bladder cancer. UptoDate 2016

NCCN Guidelines Version 2.2016 Bladder Cancer

APPROXIMATE PROBABILITY OF RECURRENCE

Pathology	Approximate Probability of Recurrence in 5 years
Ta, low grade	50%
Ta, high grade	60%
T1, low grade (rare)	50%
T1, high grade	50% - 70%
Tis	50% - 90%

* MOLECULAR MECHANISM & GENETICS

- TP53
- RB1
- PTEN
- FGFR3
- PIK3CA
- HRAS
- TSC1
- TERT

- GSTM-1
- NAT-2
- LOH of 9p
- Homozygous deletion of CDKN2A
- Loss of expression of p16

PRESENTATION & DIAGNOSIS

- The most common presenting symptom is **painless hematuria**
- Rate of urinary tract malignancy in asymptomatic microhematuria < 3%

- Urinary cytology
- Bimanual exam
- Imaging
  - CT with IV contrast
  - MRI with gadolinium
  - Retrograde pyelogram
  - (Intravenous urography)

- Diagnosis confirmed by Cystoscopy/ transurethral resection (TURBT)

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Urinary Marker Tests

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

9. A clinician should not use urinary biomarkers in place of cystoscopic evaluation. (AUA Guidelines 2016, Strong Recommendation; Evidence Strength: Grade B)

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* Performance of Urinary Marker Tests

Table 3 Measured and published sensitivity and specificity for each test in the integrated dataset before imputation, mean and 95 % CIs

	Measured		Published	
	Sensitivity, % (95 % CI)	Specificity, % (95 % CI)	Sensitivity, % (95 % CI)	Specificity, % (95 % CI)
Cytology	45.5 (40.6–50.4)	96.3 (94.5–97.9)	56.1 (43.3–68.3) [18]	94.5 (91.9–96.5) [18]
NMP22	44.9 (37.4–52.3)	89.0 (86.5–91.5)	50.0 (37.4–62.6) [18]	88.0 (84.6–91.0) [18]
FISH	40.0 (22.7–52.3)	87.3 (83.7–91.6)	72 (69–75) [22]	83 (82–85) [22]
			61.9 [23]	89.7 [23]
			18 [24]	90 [24]
Cxbladder Detect	79.5 (71.1–87.8)	82.2 (79.2–85.0)	81.8 [18]	85.1 (fixed) [18]

* Cxbladder negative predictive value 97-98%

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Breen V, et al. *BMC Medical Research Methodology.* 2015;15:1-12.

Grade and Stage

- Tumor grade is an important prognostic factor for determining risk of recurrence and progression in bladder cancer.
- The WHO/ISUP 2004 grading system is now the most widely accepted and utilized system in the United States.

2004 World Health Organization/ International Society of Urologic Pathologists: Classification of Non-muscle Invasive Urothelial Neoplasia
Hyperplasia (flat and papillary)
Reactive atypia
Atypia of unknown significance
Urothelial dysplasia
Urothelial CIS
Urothelial papilloma
Papillary urothelial neoplasm of low malignant potential (PUNLMP)
Non-muscle invasive low-grade papillary urothelial carcinoma
Non-muscle invasive high-grade papillary urothelial carcinoma

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Clinical stage includes histologic findings at TURBT; physical exam, including bimanual exam under anesthesia; and findings on imaging

Staging of primary tumors (T) in bladder cancer	
TX	Primary tumor cannot be assessed
Ta	Noninvasive papillary carcinoma
Tis	Carcinoma in situ (CIS)
T1	Tumor invades lamina propria
T2	Tumor invades muscularis propria
T2a	Tumor invades superficial muscularis propria (inner half)
T2b	Tumor invades deep muscularis propria (outer half)
T3	Tumor invades perivesical tissue/fat
T3a	Tumor invades perivesical tissue/fat microscopically
T3b	Tumor invades perivesical tissue fat macroscopically (extravesical mass)
T4	Tumor invades prostate, uterus, vagina, pelvic wall, or abdominal wall
T4a	Tumor invades adjacent organs (uterus, ovaries, prostate stoma)
T4b	Tumor invades pelvic wall and/or abdominal wall

Regional Lymph Nodes (N)

Regional lymph nodes include both primary and secondary drainage regions. All other nodes above the aortic bifurcation are considered distant lymph nodes.

NX	Lymph nodes cannot be assessed
N0	No lymph node metastasis
N1	Single regional lymph node metastasis in the true pelvis (hypogastric, obturator, external iliac, or presacral lymph node)
N2	Multiple regional lymph node metastasis in the true pelvis (hypogastric, obturator, external iliac, or presacral lymph node metastasis)
N3	Lymph node metastasis to the common iliac lymph nodes

Histopathology

- Variant cell types and growth patterns
  - Squamous cell differentiation
  - Glandular differentiation
  - Small cell (neuroendocrine)
  - Signet cell
  - Sarcoma
  - Plasmacytoid cell
  - Micropapillary
  - Nested

Small Cell Carcinoma

- –<1% of bladder tumors
- Chromogranin A, synaptophysin, neuron specific enolase stains useful for diagnosis
- Poor outcomes, high relapse rates after treatment
- Treated with cisplatin/etoposide

Micropapillary

- Most commonly found in association with high grade invasive UC
- Rare component but increasingly recognized
- Associated with aggressive disease

Nested Variant

- Very rare
- Deceptively benign appearing nests of cells, suspect if “low grade, invasive”
- Thought to be more aggressive subtype with poor prognosis

Prognosis

- Cancer-specific survival (CSS) in high-grade disease ranging from approximately 70-85% at 10 years and a >95% in low-grade disease.
- **Risk stratification in NMIBC important for management**

	Risk of Progression (%)	Risk of Recurrence (%)
Low-Grade Ta	**6**	**55**
High-Grade T1	**17**	**45**

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Palou 2012; Cookson 1997; Leblanc 1999

AUA 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

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THE JOURNAL of UROLOGY®
Official Journal of the American Urological Association
AUA 2016 san diego

Diagnosis and Treatment of Non-Muscle Invasive Bladder Cancer: AUA/SUO Guideline

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

From the American Urological Association Education and Research, Inc., Linthicum, Maryland

Systematic review of all relevant published literature and 38 statements covering principles of management based on body of evidence strength, level of certainty, magnitude of benefit or risk/burdens, and the Panel's judgment

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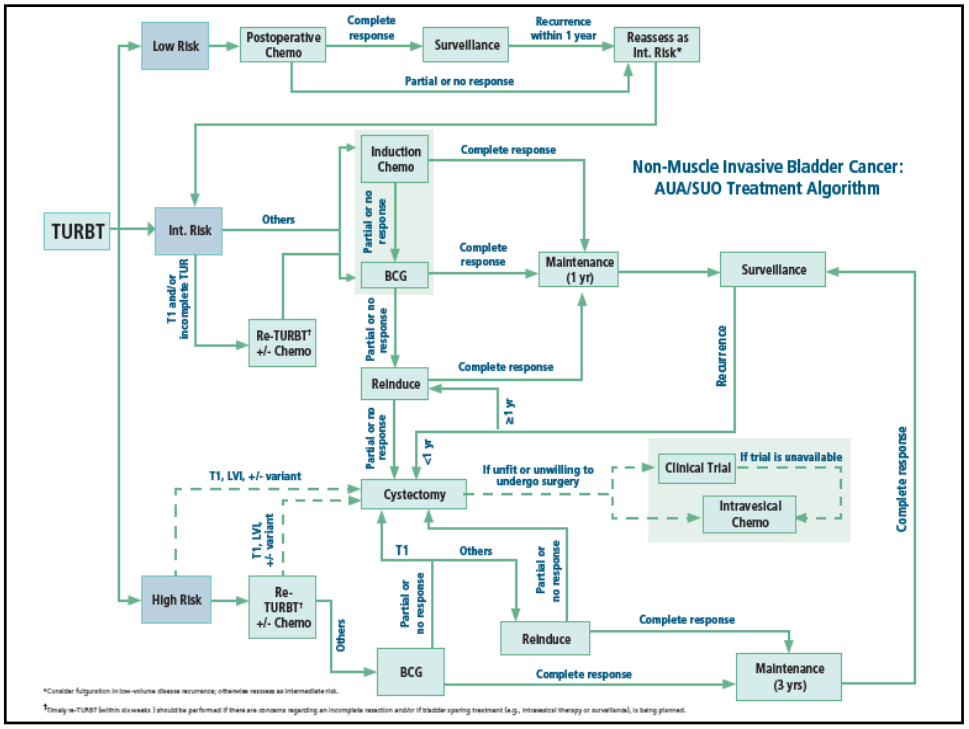
Chang SS, et al. *J Urol.* 2017 Apr 26.



NMIBC

- Papillary tumors confined to mucosa (Ta)
- Tumors involving subepithelial tissue- lamina propria (T1)
- Carcinoma in-situ (CIS)

Adjuvant Therapy

- Immediate postop intravesical chemotherapy
  - Thought to eliminate implantation of tumor cells
- Given within 24 hours after TURBT
- Randomized studies demonstrate an 11.7% decrease in recurrence rate using a single post TURBT dose of chemotherapy (mito C, doxyorubicin, epirubicin)
- Primary and solitary tumors benefit most, guideline recommendations are for all post TURBT
- –Do not give if perforation is suspected
- –NEVER give BCG in the immediate post TURBT setting

AUA 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, a clinician should consider prostatic urethral biopsies and upper tract imaging, as well as enhanced cystoscopic techniques (blue light cystoscopy, when available), ureteroscopy, or random bladder biopsies. (Expert Opinion)

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AUA Guidelines Statements

5. At the time of each occurrence/recurrence, assign a clinical stage and risk category

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AUA Guidelines- Variant Histology

6. An experienced genitourinary pathologist should review the pathology of a patient with any doubt in regards to variant or suspected variant histology (Moderate Recommendation; Evidence Strength: Grade C)

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

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AUA Guideline- Variant Histology

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

There is a lack of evidence regarding the efficacy of intravesical therapy for NMIBC with variant histology.

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AUA Guidelines Urine Markers

9. A clinician should not use urinary biomarkers in place of cystoscopic evaluation. (Strong Recommendation; Evidence Strength: Grade B)

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 intravesical BCG (UroVysion® FISH) and adjudicate equivocal cytology (UroVysion® FISH and ImmunoCyt™). (Expert Opinion)

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AUA Guidelines- TURBT

12. If incomplete initial resection, perform repeat TURBT if technically feasible. (Strong Rec; Grade B)

13. HG Ta tumors- should consider repeat TURBT within 6 weeks (Mod Rec; Grade C)

14. T1 disease- should repeat TURBT to include muscularis propria within 6 weeks (Strong Rec; Grade B)

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AUA Guidelines- TURBT

15. Low- or intermediate-risk bladder cancer-

    should consider administration of a **single postoperative instillation of intravesical chemotherapy (e.g., mitomycin C or epirubicin) within 24 hours of TURBT** unless suspected perforation or extensive resection. (Mod Rec; Grade B)

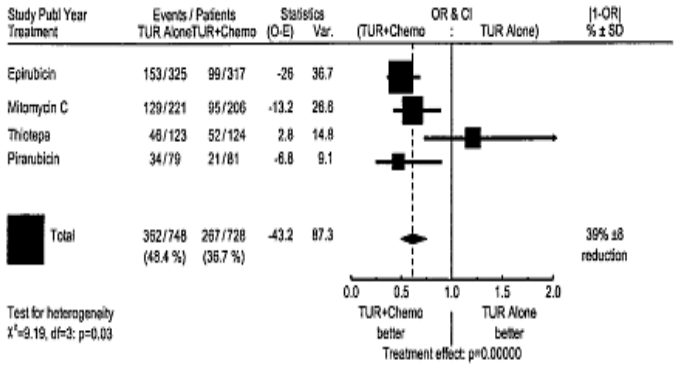

FIG. 2. Forest plot of recurrence by treatment

Sylvester 2004

AUA Guidelines- Intravesical therapy

16. In a low-risk patient, a clinician should not administer induction intravesical therapy. (Mod Rec; Grade C)

17. In intermediate-risk- 6 week course of induction intravesical chemotherapy or immunotherapy. (Mod Rec; Grade B)

18. In a high-risk patient with newly diagnosed CIS, high-grade T1, or high-risk Ta urothelial carcinoma- 6 weeks course of BCG. (Strong Rec; Grade B)

*AUA Guidelines- Intravesical Therapy

- **There is insufficient evidence to recommend one particular strain of BCG**
  - Several small studies suggest that different strains may have different efficacies
- **There is insufficient evidence to prescribe a particular strength of BCG**
  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**
  - Several ongoing trials are currently examining synergistic combinations

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Rentsch 2014; Oddens 2013; Houghton 2013

AUA Guidelines- 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 Rec; Grade C)

20. In an intermediate-risk patient who completely responds to induction BCG, a clinician 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, a clinician should continue maintenance BCG for three years, as tolerated. (Moderate Recommendation; Evidence Strength: Grade B)

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Rentsch 2014; Oddens 2013; Houghton 2013

AUA Guidelines- BCG Relapse

22. In an intermediate- or high-risk patient with persistent or recurrent disease or positive cytology following intravesical therapy, a clinician should consider performing prostatic urethral biopsy and an upper tract evaluation prior to administration of additional intravesical therapy. (Conditional Rec; 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. (Mod Rec; Grade 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. (Mod Rec; Grade C)

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AUA Guidelines- BCG Relapse

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, non-muscle-invasive disease and/or CIS within six months of two induction courses of BCG or induction BCG plus maintenance. (Mod Rec; Grade C)

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

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AUA Guidelines- Cystectomy

27. In a patient with Ta low- or intermediate-risk disease, a clinician 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 histologies, a clinician should consider offering initial radical cystectomy. (Mod Rec; 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, a clinician should offer radical cystectomy. (Mod Rec; Grade C)

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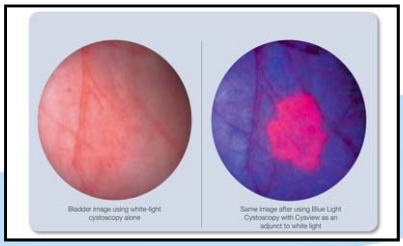
AUA Guidelines- Enhanced Cystoscopy

30. -Should offer blue light cystoscopy at the time of TURBT, if available, to increase detection and decrease recurrence. (Mod Rec; Grade B)

31. -may consider use of NBI to increase detection and decrease recurrence. (Conditional Rec; Grade C)



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Daneshmand, Nature Reviews Urology 2014

AUA Guidelines- Surveillance

32. After initial evaluation and treatment, first surveillance cystoscopy within 3-4 months. (Expert Opinion)

33. For a low-risk patient whose first surveillance cystoscopy is negative for tumor, a clinician 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, a clinician should not perform routine surveillance upper tract imaging. (Expert Opinion)

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AUA Guidelines- Surveillance

35. -History of low-grade Ta disease and a noted sub-centimeter papillary tumor(s), a clinician may consider in-office fulguration (Expert Opinion)

36. -intermediate-risk patient with negative first surveillance cystoscopy: Surveillance cystoscopy with cytology every 3-6 months for 2 years, then 6-12 months for years 3 and 4, and then annually thereafter. (Expert Opinion)

37. -High-risk patient with negative first surveillance cystoscopy, subsequent cystoscopy with cytology every 3-4 months for 2 years, then 6 months for 3-4 years and then annually thereafter. (Expert Opinion)

38. For an intermediate- or high-risk patient, a clinician should consider performing surveillance upper tract imaging at 1-2 year intervals. (Expert Opinion)

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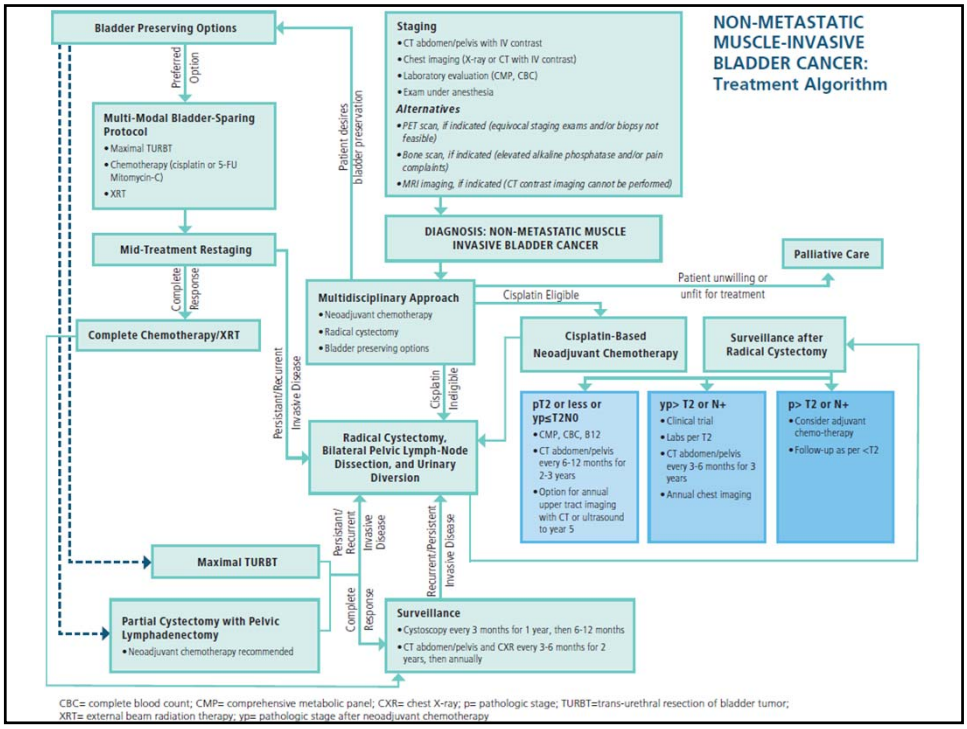

Staging

- The reported rate of post-surgical upstaging to EV disease is as high as 40%
- The false negative rate regarding nodal staging is even higher, up to 68%
- Hydronephrosis strong predictor of upstaging to extravesical disease and independent predictor of worse prognosis

Imaging

- **CT with IV contrast or MRI**
  - Evaluate upper tracts, lymphadenopathy
- **Need chest imaging** to rule out metastatic disease
- **PET scan**
  - 70% sensitivity and 90% specificity for LN mets not identified on CT or MRI
  - Limited in primary bladder stage- FDG pooled in bladder
- **Bone scan** only if clinically indicated (bone pain, ↑alk phos)

Treatment

- Gold standard remains surgery +/- neoadjuvant chemotherapy
- Radical cystectomy
- Mainstay of local/regional therapy
  - Male: bladder, the perivesical fat, the prostate, the seminal vesicles and the prostatic urethra.
  - Female: (anterior pelvic exenteration): bladder, uterus, cervix, fallopian tubes, ovaries and the anterior vagina.

Radical Cystectomy- Male

- Male: ~50% chance of cancer involvement of the prostate (either urothelial carcinoma or adenocarcinoma of the prostate)
- Total urethrectomy is rarely required
  - Vast majority of cases a negative urethral margin can be achieved
  - Pts with + urethral margin on final pathology can be considered for delayed urethrectomy
- A randomized trial showed no difference in complication rates between open and robotic cystectomy.

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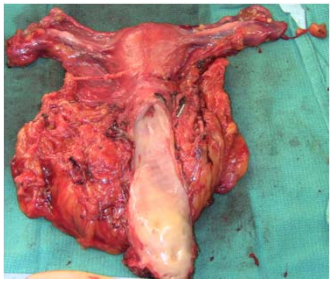
Bruins, Daneshmand :*J Urol.* Nov 2013
Bochner et al. European Eur 2015)

Radical Cystectomy-Female



- Reproductive organs often removed
  - Risk of involvement <10%
  - Vagina most commonly involved site
- Patients with low stage disease can be considered for vaginal sparing or female organ preserving techniques, which can potentially improve post-operative sexual function
  - Risk of positive margin posteriorly

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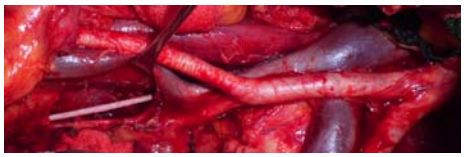
Djaladat, Daneshmand: j Urol Dec 2012
AUA Guidelines, 2017

Lymph Node Dissection



- Anatomic lymph node drainage:
  - Perivesical lymphatic tissue
  - internal and external iliac lymphatic chains
  - Common iliacs
  - Aortic bifurcation
  - Presacral, presciatic (fossa of Marcilles)
  - Para-aortic/paracaval
- "Skip" LN mets possible
- A meticulous and thorough **pelvic lymph node dissection** must be performed at time of radical cystectomy
  - accurately staging
  - Improved survival with thorough lymph node dissection
  - Extent remains controversial - **At minimum Standard LND**

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Hugen, Daneshmand WJU 2015
AUA Guidelines, 2017

* Necessity of Mechanical Bowel Prep

- No evidence to show mechanical bowel prep reduces anastomotic leak
- No difference in
  - Mortality, Morbidity, Peritonitis, Re-operation, Surgical site infection, Wound Infection, Fistula, Sepsis.
- Lower incidence of ileus and shorter hospital stay in the no bowel prep group

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Shafii et al. BJU Int 2002

* Necessity of Nasogastric Tube

– Patients <u>without NGT</u>

- Significantly less fever, atelectasis, pneumonia, days to 1st oral intake, shorter time to first flatus, shorter hospitalization
- No increased risk of ileus, bowel obstruction, wound dehiscence, anastomotic leak, or aspiration pneumonia

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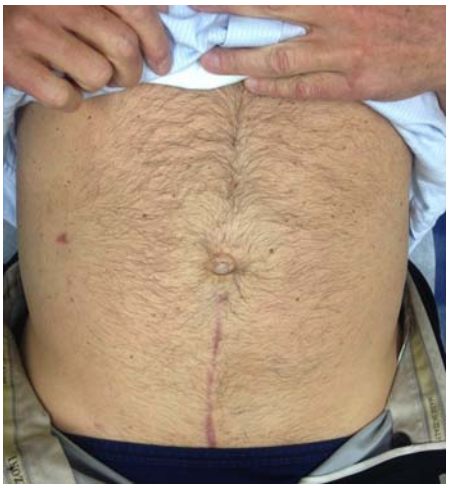
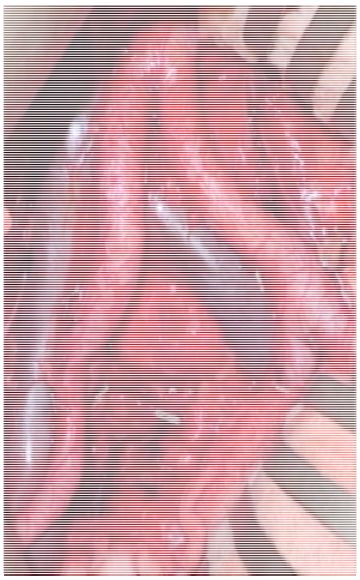
Cheatham et al. Ann Surg (1995),
Inman et al. J Urol (2003)

Enhanced Recovery After Surgery- ERAS





Peri-operative Management- Enhanced Recovery After Surgery (ERAS)

15. Optimization of patient performance status in accordance with ERAS principles
  - –Nutritional counseling
  - –Smoking cessation
  - –Bowel preparation

16. Pharmacologic thromboembolic prophylaxis –AUA Best Practice Statement on the Prevention of Deep Vein Thrombosis

- **Alvimopan- mu receptor antagonist**
  - Decreases ileus, LOS in multiple randomized trials

Others:

- Avoidance of NG tubes
- Avoidance of bowel preparation
- Enforced early enteral feeding starting on POD#1

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Median Hospital Stay 4 days- Daneshmand et al . Enhanced Recovery Protocol Following Radical Cystectomy, J Urology 2014

*Radical Cystectomy- Outcomes

- Disease free survival 5-10 year
  - <pT1: 85%
  - pT2: 75%
  - pT3: 45-50%
  - pT4: 35%
  - N+: 25-33%
- Outcomes effected by
  - Stage
  - LN status
  - margin status
  - LVI
- Perioperative mortality (1-2%) *
  - * 2-3X higher in community hospitals with less experience
- Complication rate 60-70%
  - Major complication rate 10-15%

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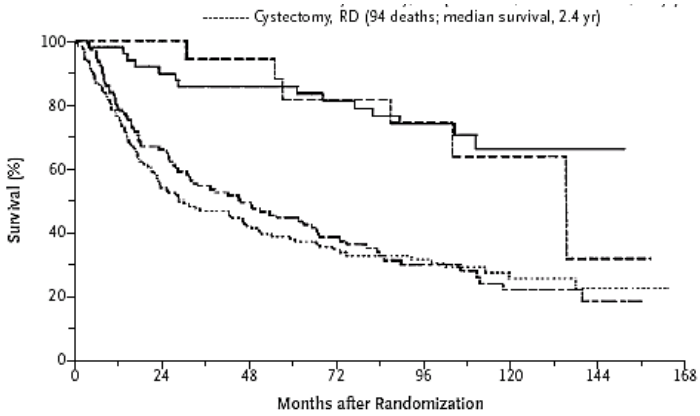
Local Recurrence

- Associated with margin status
- Median time to local recurrence 8-18 mos
- Symptoms: pain (pelvic, perineal, lower extremity); bleeding; lower extremity or penile edema; bowel obstruction; constipation or priapism
- Treated with chemo +/- XRT, Immunotherapy
- Median survival 4-8 months

Neoadjuvant Chemotherapy

- Improves survival (level 1 evidence): 5% absolute improvement in survival found in randomized studies
- 14-25% reduction in risk of dying of bladder cancer in patients treated with neoadjuvant chemotherapy

SWOG 8710: Survival by Pathologic Stage at Cystectomy



No. at Risk							
M-VAC and cystectomy, pT0	48	43	40	37	26	12	2
Cystectomy, pT0	18	17	15	12	10	4	1
M-VAC and cystectomy, RD	105	69	52	38	20	11	4
Cystectomy, RD	136	71	52	37	27	14	6

TREATMENT: CHEMOTHERAPY (AUA Guidelines)

Cisplatin-based NAC to eligible radical cystectomy patients prior to cystectomy

- *No validated predictive factors or clinical characteristics associated with probability of response and benefit using cisplatin-based NAC*
- *The best regimen and duration for cisplatin-based NAC remains undefined*
- *The decision regarding eligibility for cisplatin-based NAC should be based on comorbidities and performance status*

Adjuvant Chemotherapy

- Recommended for ≥ pT3, or N+ disease
- No Level 1 evidence available
- Trials hampered by poor accrual
- Meta-analysis shows survival benefit

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Bladder Preservation Strategies

- Radical transurethral resection
- Partial cystectomy
- Radiation therapy
  - With systemic chemotherapy
  - Without systemic chemotherapy
- Systemic chemotherapy

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Radical TURBT: 10-yr Outcomes

Author	Herr*		Solsona	
Outcome at	***5 yr***	***10 yr***	***5 yr***	***10yr***
%Overall survival	76	57	74	40
% cancer specific survival	82	75	82	80

*Initial TURBT followed by aggressive repeat TURBT
If no MIBC noted, observation alone
Visually complete TURBT followed by multiple biopsies (>5) of deep muscle and perivesical fat Herr JCO 2001, Solsona J Urol 2010

Partial Cystectomy

- Optimal candidates
  - Urachal cancer, adenocarcinoma
  - smaller lesions, unifocal,
  - Location at dome or region away from ureteral orifices, diverticula
  - No associated CIS
- Removal with negative margin required
  - Should still undergo bilateral PLND
- Overall 5-year survival up to 69%
- Local recurrence in up to 50% so lifelong surveillance required

Holzbeierlein JM, *J Urol.* Sep 2004

Radiation

- Usually administered along with radio-sensitizing single agent chemotherapy
  - Cisplatin most common
  - Gemcitibine, 5FU also may be used
- Trimodal approach requires radical TURBT (maximal debulking)
- Best candidates: smaller lesions, earlier stage, no hydronephrosis best candidates
- Not effective against CIS of the bladder

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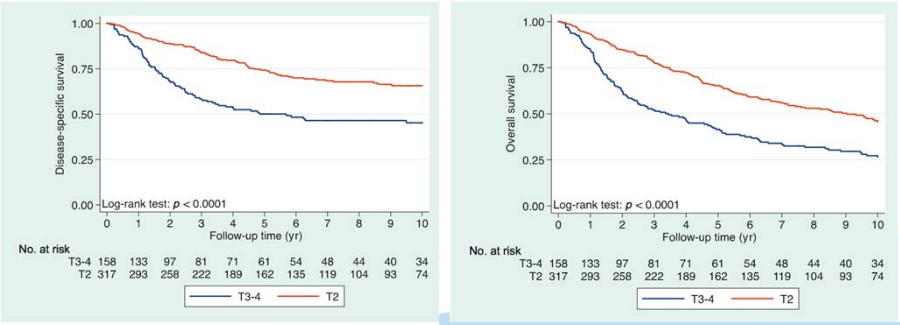
Trimodality Therapy for Bladder Cancer-Updated Mass Gen Hospital Experience



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Giacalone NJ, et al. *Eur Urol*. 2017;71:952-960.

Gemcitabine/Cisplatin (GC) vs. MVAC in Metastatic Bladder Cancer

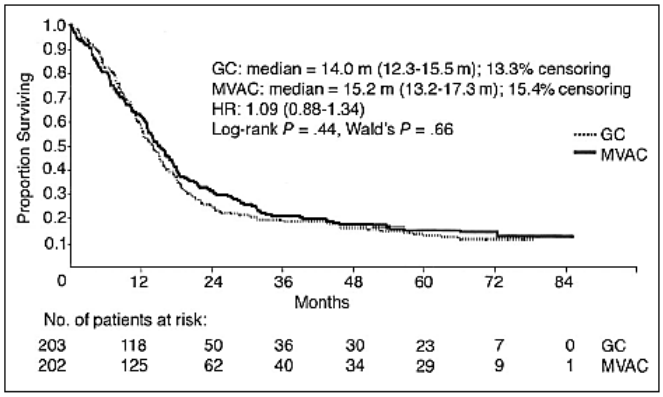

Fig 1. Kaplan-Meier curves for overall survival. GC, gemcitabine/cisplatin; MVAC, methotrexate/vinblastine/doxorubicin/cisplatin; HR, hazard ratio; Pts, patients.

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Von Der Masse, JCO 2005

Metastatic Disease

- Poor prognosis (median survival about 1 year)
- Chemotherapy
  - MVAC (methotrexate, vinblastine, Adriamycin [doxorubicin], and cisplatin)
  - Dose-dense MVAC (ddMVAC)
  - Gemcitabine + cisplatin (Gem-Cis)
    - comparable efficacy but less toxic than MVAC (but not necessarily ddMVAC)
  - Carbo/Gem alternative in cisplatin ineligible patients
    - Less efficacious than Gem/Cis

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* Chemotherapy- Toxicity

- **Cisplatin**
  - Binds DNA and produces intra-strand crosslinks and DNA adducts, thus inhibiting DNA replication
  - **Nephrotoxicity**
  - **Ototoxicity**
- **Gemcitabine**
  - cytidine analog that inhibits DNA synthesis
  - **Myelosuppression**
- **Carboplatin**
  - Does not require prolonged hydration and extensive anti-emetic premedications.
  - **Bone marrow suppression**
  - **Thrombocytopenia**
- **Taxanes**
  - Some response in 2nd line
  - **Peripheral neuropathy**
  - **myelosuppression**.

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Efficacy of PD-1 or PD-L1 Immune Checkpoint Inhibitors in Advanced Bladder Cancer

Study	Pts	Previous Platinum?	Comparator Drug	ORR	OS (mo)
Atezolizumab (IMvigor 210)	310	Yes	No	All: 15% IC0: 8% IC1: 10% IC2/3: 26%	All: 7.9
Atezolizumab (IMvigor 210)	119	No, first-line**	No	All: 19% IC1/2/3: 19% IC2/3: 22%	All: 10.6
Avelumab	241	Yes	No	PD-L1 (-): 14.7% PD-L1 (+): 25%	PD-L1 (-) 6-month OS: 52.7% PD-L1 (+) 6-month OS: 61.2%
Durvalumab	103	Yes	No	PD-L1 (-): 5.1% PD-L1 (+): 31.1%	Not Published
Nivolumab (CheckMate-275)	265	Yes	No	All: 19.6% PD-L1 (-): 16.1% PD-L1 >1%: 23.8% PD-L1 >5%: 28.4%	All: 8.74 PD-L1 (-): 59.95 PD-L1 >1%: 11.3
Nivolumab (CheckMate-032)	78	Yes	No	All: 24.4% PD-L1 (-): 26.2% PD-L1 (+): 24%	All: 9.7 PD-L1 (-): 9.9 PD-L1 (+): 16.2
Pembrolizumab (KEYNOTE-045)	542	Yes	Paclitaxel, docetaxel, or vinflunine	All: 21.1 vs. 11.4% PD-L1 (+): 21.6 vs. 6.7%	All: 10.3 vs 7.4 PD-L1 (+): 8 vs 5.2
Pembrolizumab (KEYNOTE-052)	100/374	No, first-line**	No	All: 24% PD-L1 (+): 37%	6-month OS: 67%