Multidisciplinary Management of Bladder Cancer: Improving Guideline-Concordant Care

Chelsea Osterman, MD

Genitourinary Medical Oncologist

Mission Medical Oncology, Asheville, NC

DISCLOSURE OF CONFLICTS OF INTERESTS

Chelsea Otterman, MD, has the following financial relationships to disclose:

- Consultant: Pfizer/Myovant Science

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OBJECTIVES

- Summarize NCCN guidelines for management of muscle-invasive bladder cancer
- Discuss disparities in bladder cancer care and potential ways to mitigate these
- Explain how a multi-disciplinary team can improve guideline-concordant care

BLADDER CANCER BY THE NUMBERS

- Estimated 81,180 new cases in the US diagnosed in 2022[1]
  - Majority (~75%) will be non-muscle invasive at diagnosis
- 6th most common cancer in the US
- Median age at diagnosis is 73
- Most common risk factor is cigarette smoking

1. Cancer Stat Facts: Bladder cancer, National Cancer Institute

DISPARITIES IN BLADDER CANCER

- White males have highest incidence of bladder cancer, however females and African Americans have more advanced stage tumors at initial diagnosis[2]
  - Appears to be true even when accounting for differences in access to care[3]
  - May be in part related to delay in time from initial symptom presentation to bladder cancer diagnosis
- Black and female patients have significantly lower odds of receiving guideline-based treatment as compared with White and male patients[4]

2. Daneshmand, 2022
3. Danforth, 2020
4. Washington, 2019

MULTI-DISCIPLINARY TEAM MEMBERS

- Primary care
- Urology
- Medical Oncology
- Radiation Oncology
- Nurse navigator
- Ostomy nurse
- Dietician
- Physical therapist
- Social work
- Financial counselor

CASE PRESENTATION

MEETING MR. SMITH

- 75 year old man with medical history including HTN and DM2.
- Former smoker with 50 pack year history, quit about 5 years ago
- Initially presents to his PCP with 1 week of painless hematuria
- Urinalysis performed and notable for > 100 RBCs, urine culture with no growth. Referred to Urology for additional work up

- Potential gaps:
- Lack of recognition of bladder cancer as possible cause of painless hematuria
  - Important to work with PCPs, urgent care, and ER providers to increase education
- Timely referral to urology
  - Black and female patients more likely to have delay in seeing urology
  - Female patients frequently referred to Ob/Gyn first
  - Delay in urology referral leads to delay in ultimate diagnosis

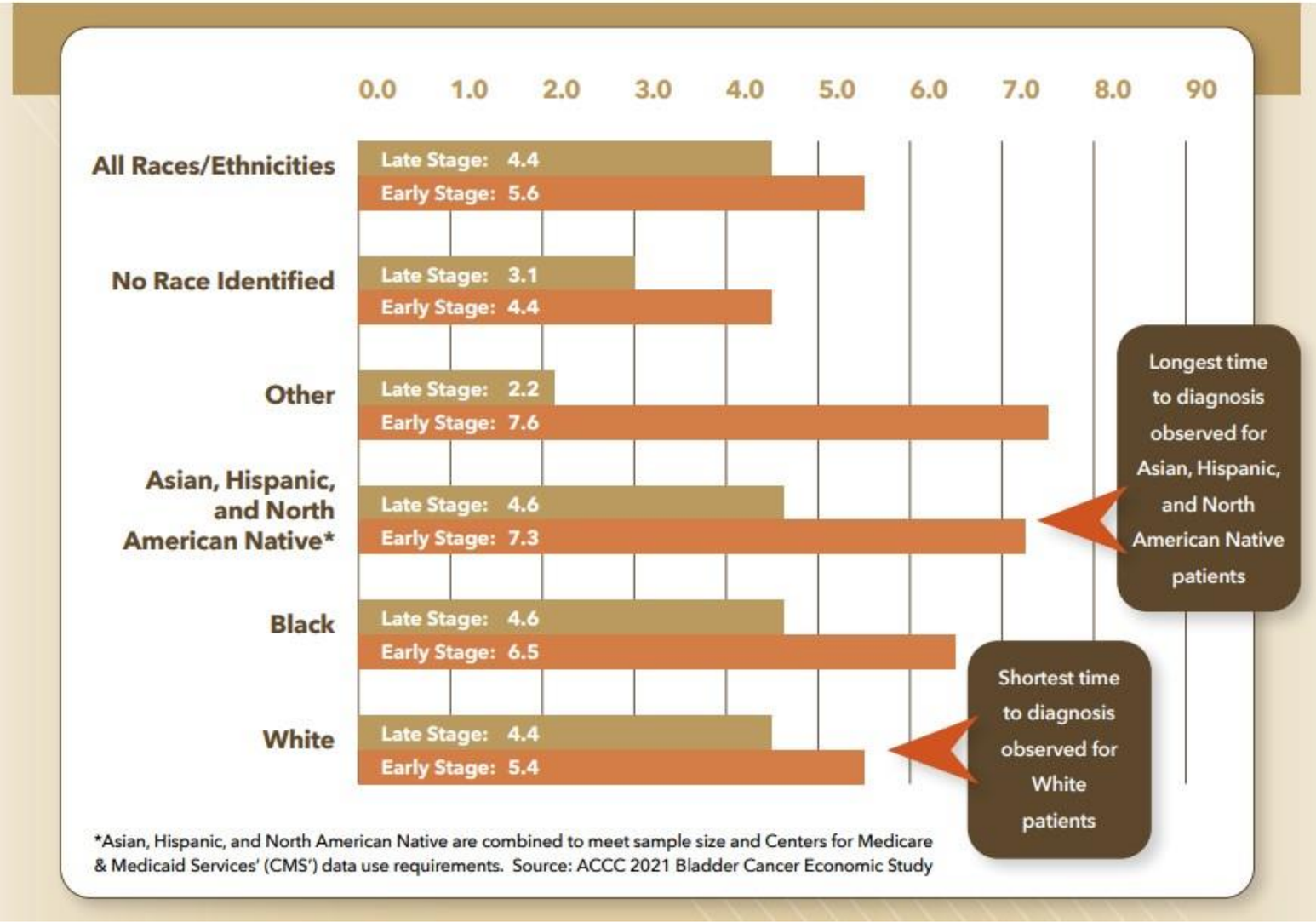
UROLOGY EVALUATION

- CT urogram reveals a 4cm mass in the bladder with perivesicular stranding concerning for possible extension of disease. No evidence of pelvic adenopathy, no hydronephrosis (cT3 cN0)
- Office cystoscopy with papillary bladder tumor
- Trans-urethral resection of bladder tumor (TURBT) performed under anesthesia. Pathology with high-grade urothelial carcinoma invading muscularis propria
- Patient referred to medical oncology

- Potential gaps:
- Lack of access to urology and/or high travel burden
  - Over 2,000 counties in the US do not have a urologist[5]
  - Even where there are urologists, few perform cystectomies regularly
- Financial difficulties, including lack of health insurance
  - Financial counselors vital to helping patients afford care, including applying for medicare/medicaid

5. Odisho, 2010

FIGURE 2. Average Time from Hematuria Diagnosis to Bladder Cancer Diagnosis (30-Day Months) by Race/Ethnicity



6. Understanding and mitigating disparities in bladder cancer care, 2022

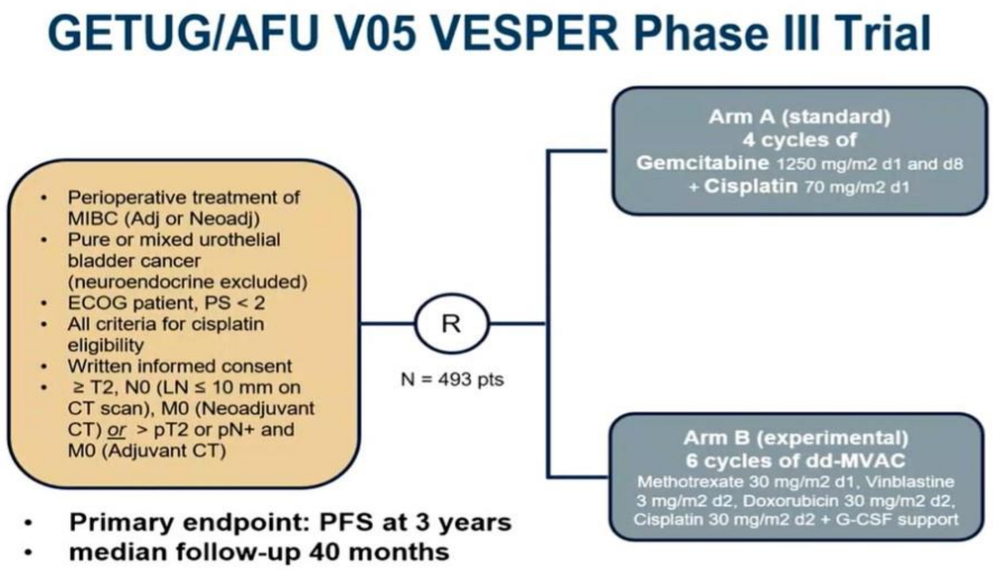
MEDICAL ONCOLOGY EVALUATION

- CT chest to complete staging with no evidence of metastatic disease
- CBC and CMP notable for mild anemia with hemoglobin of 12, good renal function with BUN 9 and creatinine 0.8

- Potential gaps:
- Use of neoadjuvant chemotherapy remains sub-optimal
  - Engage with local urologists to develop treatment pathway that includes referrals to both medical and radiation oncology for all patients with MIBC
  - Utilize nurse navigators to help coordinate care
  - Co-localization of providers across specialties can allow patients to have multiple visits scheduled in one day and minimize time/cost of traveling
  - Consider 24 hour urine for creatinine clearance evaluation in patients with borderline renal function
  - Consider nephrostomy tube placement for patients with tumor-related hydronephrosis with repeat evaluation of renal function afterwards

NEOADJUVANT CHEMOTHERAPY

- GETUG/AFU V05 VESPER Trial:
- 58% of patients fully completed planned 6 cycles ddMVAC, 66% fully completed 4 cycles GC
- In neoadjuvant group, 3 year PFS 66% with ddMVAC vs 56% with GC (HR 0.70; 95% CI 0.51-0.96)
- ddMVAC significantly improved OS in neoadjuvant group (HR 0.66; 95% CI 0.47-0.92)



	GC	dd-MVAC	*p* value
	(*n* = 198)	(*n* = 199)	
Complete response			
ypT0 pN0	71 (36%)	84 (42%)	0.021
ypTis or ypTa or ypT1 and ypN0		42 (21%)	
≥ypT2 and ypN0	63 (32%)	51 (26%)	
ypN+	35 (18%)	20 (10%)	
Uncertain staging	2	2	
Non-muscle invasive			
<ypT2 pN0	98 (49%)	126 (63%)	0.007
≥ypT2 or ypN+	99 (50%)	72 (36%)	
Uncertain staging	1	1	
Organ-confined disease			
<ypT3 pN0	124 (63%)	154 (77%)	0.001
≥ypT3 or ypN+	73 (37%)	43 (22%)	
Uncertain staging	1	2	

7. Pfister, 2022

VARIANT HISTOLOGY

- Urothelial carcinoma with component of variant histology usually treated like pure urothelial
- Micropapillary, plasmacytoid, and sarcomatoid tend to be more aggressive
  - Plasmacytoid often has loss of e-cadherin expression with CDH1 mutation, tendency for developing peritoneal carcinomatosis
  - Consider upfront cystectomy for T1 disease with these variants due to high risk of progression
- For localized disease with any small cell/neuroendocrine component, recommend neoadjuvant cis/carboplatin + etoposide with either cystectomy or RT as consolidation
- Pure squamous cell- no clear role for neoadjuvant or adjuvant systemic therapy
- Pure adenocarcinoma- important to distinguish between urachal vs primary bladder adenocarcinoma
  - Also important to evaluate for colorectal primary
  - Urachal adenocarcinoma often amenable to partial cystectomy, should be performed with en bloc resection of the urachal ligament and umbilicus with LND
  - No clear role for neoadjuvant or adjuvant systemic therapy

URACHAL ADENOCARCINOMA

RADIATION ONCOLOGY EVALUATION

- Tri-modality therapy (TMT) includes maximal TURBT followed by concurrent chemoRT
- "Ideal" TMT candidates:
  - Pure urothelial histology
  - Absence of extensive CIS
  - cT2-3a disease with unifocal tumor < 5cm
  - Absence of tumor-associated hydronephrosis
  - "A bladder worth sparing"
- Potential gaps:
- Patients not always referred to radiation oncology or counseled on bladder-sparing protocols
- Initial TMT and post-treatment surveillance requires extensive coordination between urology, medical oncology, and radiation oncology.
- Initial course of chemoRT can require significant travel for many patients, which can also have high financial burden

BACK TO MR. SMITH

- Receives neoadjuvant chemotherapy with gemcitabine + cisplatin x 4 cycles
- Repeat CT CAP with decreased size of bladder tumor, no pathologic adenopathy, no evidence of distant metastatic disease
- Proceeds with radical cystoprostatectomy with ileal conduit. Pathology with ypT2 ypN0

CYSTECTOMY TIMING

- In patients who do not receive neoadjuvant chemotherapy, delay of > 12 weeks from diagnosis to cystectomy associated with higher mortality[8]
  - Men, rural patients, and patients with lower socioeconomic status more commonly experience delays in time to cystectomy[9]
- For patients who do receive neoadjuvant chemotherapy, important to coordinate urology follow up to facilitate timely cystectomy
  - Aim for cystectomy within 10 weeks of completing chemotherapy[10]

8. Gore, 2009
9. Chu, 2019
10. Alva, 2011

ADJUVANT THERAPY

- CheckMate 274 Trial:
- Included 709 patients with urothelial carcinoma at high risk for recurrence
  - ypT2-4a or ypN+ for patients who received neoadjuvant cisplatin
  - pT3-4a or pN+ for patients ineligible for/declining adjuvant cisplatin
- Randomized to nivolumab 240mg IV q2 weeks vs. placebo for up to 1 year
- Median DFS 20.8 months with nivolumab vs 10.8 months with placebo

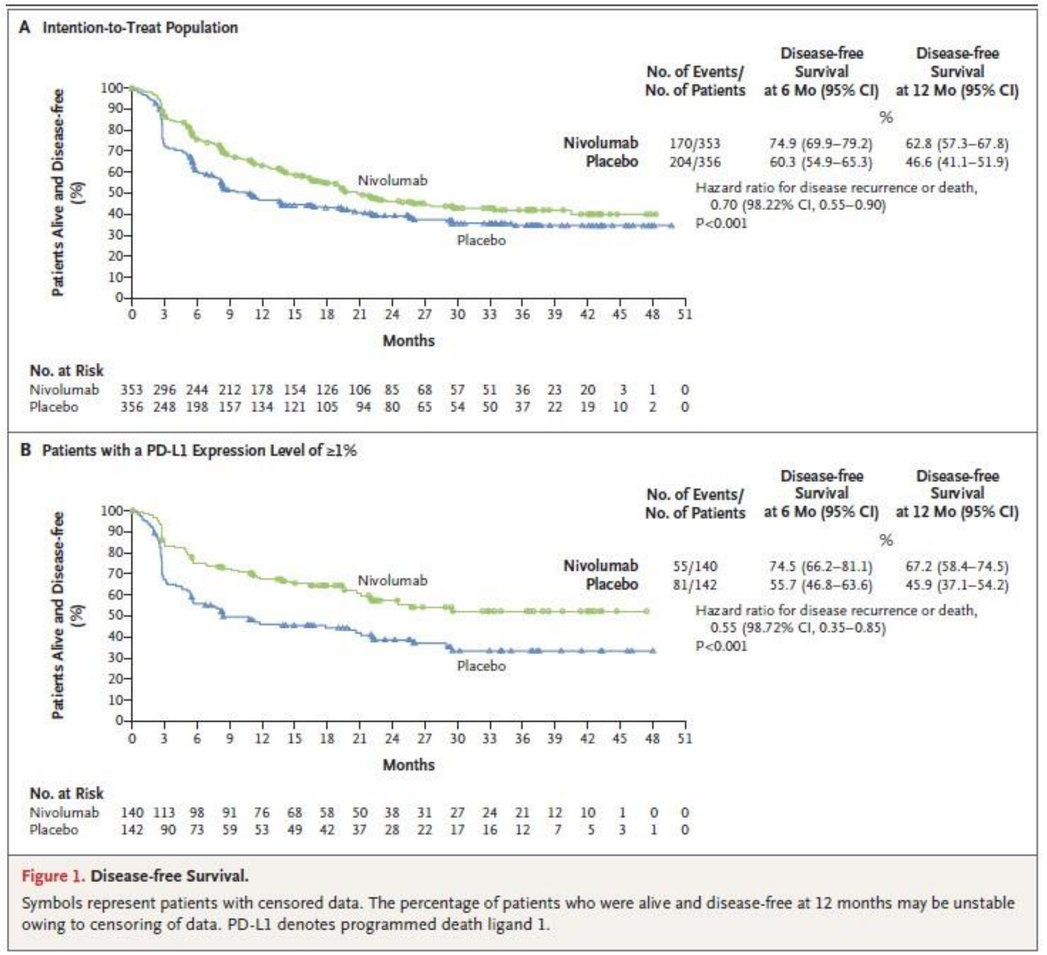


Figure 1. Disease-free Survival.

Symbols represent patients with censored data. The percentage of patients who were alive and disease-free at 12 months may be unstable owing to censoring of data. PD-L1 denotes programmed death ligand 1.

11. Bajorin, 2021

CTDNA

- IMvigor010 trial of adjuvant atezolizumab versus observation did not meet its primary endpoint
  - Median DFS 19.4 months with atezolizumab versus 16.6 months with observation (HR 0.89, 95% CI 0.74 – 1.08)

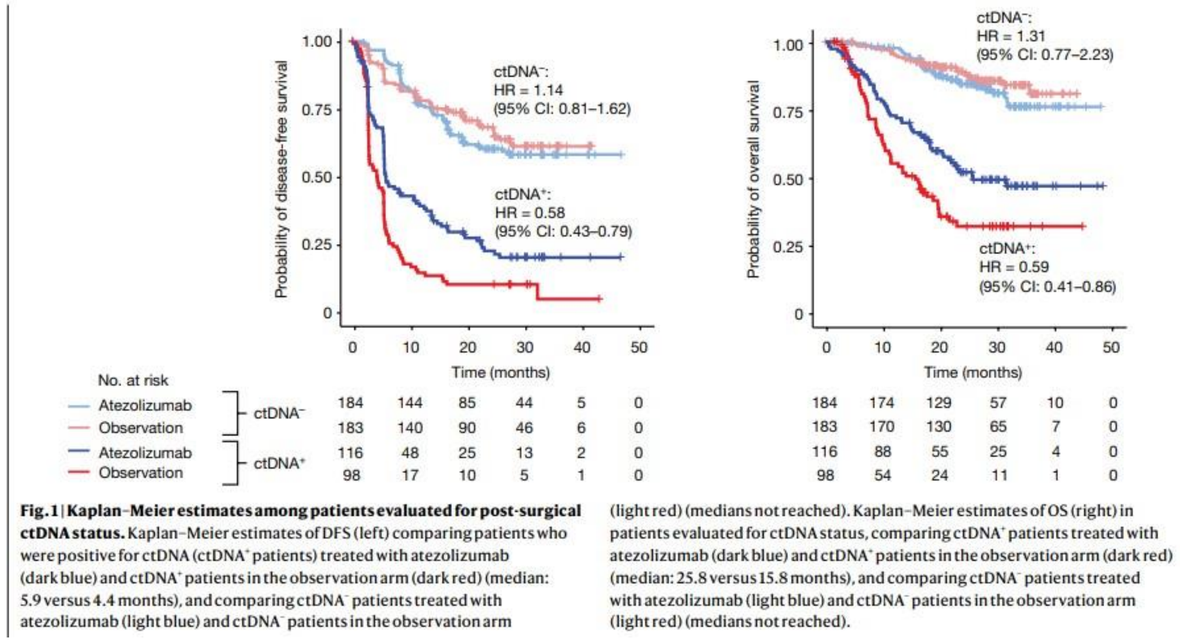


Fig. 1 | Kaplan–Meier estimates among patients evaluated for post-surgical ctDNA status. Kaplan–Meier estimates of DFS (left) comparing patients who were positive for ctDNA (ctDNA⁺ patients) treated with atezolizumab (dark blue) and ctDNA⁺ patients in the observation arm (dark red) (median: 5.9 versus 4.4 months), and comparing ctDNA⁻ patients treated with atezolizumab (light blue) and ctDNA⁻ patients in the observation arm (light red) (medians not reached). Kaplan–Meier estimates of OS (right) in patients evaluated for ctDNA status, comparing ctDNA⁺ patients treated with atezolizumab (dark blue) and ctDNA⁺ patients in the observation arm (dark red) (median: 25.8 versus 15.8 months), and comparing ctDNA⁻ patients treated with atezolizumab (light blue) and ctDNA⁻ patients in the observation arm (light red) (medians not reached).

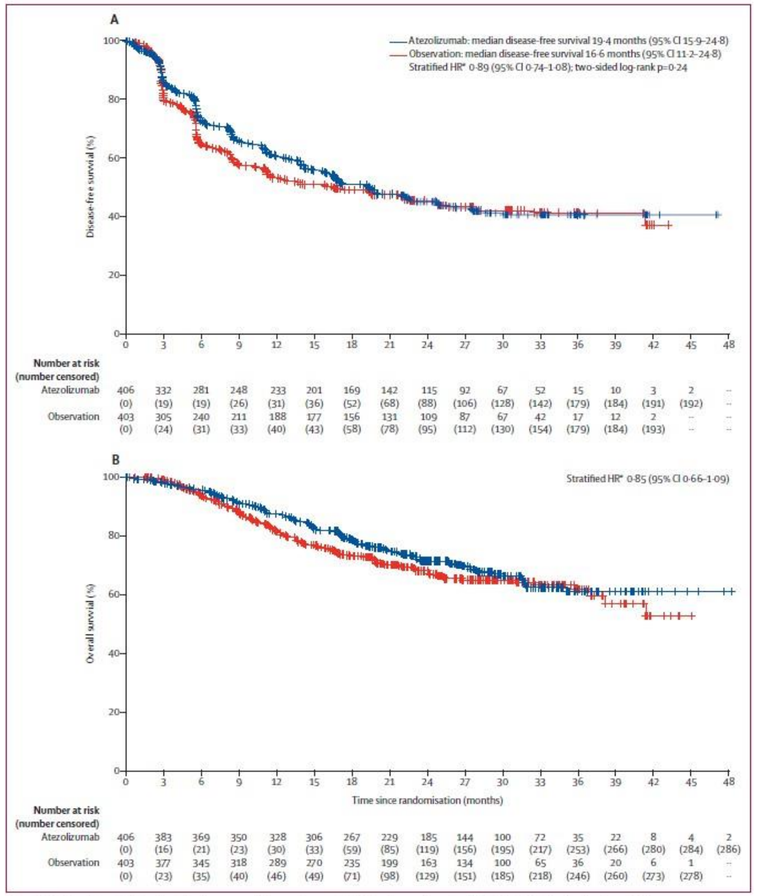


Figure 2: **Kaplan-Meier plots for investigator-assessed disease-free survival (A) and overall survival (B) in the intention-to-treat population**
HR=hazard ratio. *Stratified by post-resection tumour stage, nodal status, and PD-L1 status.

12. Bellmunt, 2021
13. Powles, 2021
14. Christensen, 2019

SURVEILLANCE

Table 6: Post-Cystectomy Muscle Invasive Bladder Cancer

Test	Year						
	1	2	3	4	5	5–10	>10
Cystoscopy	N/A						
Imaging[4]	• CTU or MRU (image upper tracts + axial imaging of abdomen/pelvis) every 3–6 mo • CT chest (preferred) or chest x-ray every 3–6 mo or • FDG PET/CT (category 2B) only if metastatic disease suspected		• Abdominal/pelvic CT or MRI annually • CT chest (preferred) or chest x-ray annually or • FDG PET/CT (category 2B) only if metastatic disease suspected			Renal US annually[6]	As clinically indicated
Blood tests	• Renal function testing (electrolytes and creatinine) every 3–6 mo • LFT[7] every 3–6 mo • CBC, CMP every 3–6 mo if received chemotherapy	• Renal function testing (electrolytes and creatinine) annually • LFT[7] annually • B_{12} annually				B_{12} annually	
Urine tests	• Urine cytology[5] every 6–12 mo • Consider urethral wash cytology every 6–12 mo[8]		Urine cytology as clinically indicated Urethral wash cytology as clinically indicated				

Table 7: Post-Bladder Sparing (ie, Partial Cystectomy or Chemoradiation)

Test	Year						
	1	2	3	4	5	5–10	>10
Cystoscopy	Every 3 mo		Every 6 mo		Annually		As clinically indicated
Imaging[4]	• CTU or MRU (image upper tracts + axial imaging of abdomen/pelvis) every 3–6 mo for MIBC • CT chest (preferred) or chest x-ray every 3–6 mo for MIBC or • FDG PET/CT (category 2B) only if metastatic disease suspected		• Abdominal/pelvic CT or MRI annually • CT chest (preferred) or chest x-ray annually or • FDG PET/CT (category 2B) only if metastatic disease suspected[9]			As clinically indicated	
Blood tests	• Renal function testing (electrolytes and creatinine) every 3–6 mo • LFT[7] every 3–6 mo • CBC, CMP every 3–6 mo if received chemotherapy	• Renal function testing (electrolytes and creatinine) as clinically indicated • LFT[7] as clinically indicated					
Urine tests	Urine cytology[5] every 6–12 mo		Urine cytology[5] as clinically indicated				

15. NCCN Bladder Cancer, 2022

THANK YOU

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