Oncology Clinical Pathways
Bladder Cancer (Urothelial Carcinoma Only)

April 2025 – V2.2025

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Bladder Cancer – Presumptive Conditions

VA automatically presumes that certain disabilities were caused by military service. This is because of the unique circumstances of a specific Veteran's military service. If a presumed condition is diagnosed in a Veteran within a certain group, they can be awarded disability compensation.

Vietnam Veterans – Agent Orange Exposure or Specified Locations

- Bladder cancer

Atomic Veterans – Exposure to Ionizing Radiation

- Cancer of the urinary tract

Gulf War and Post 9/11 Veterans

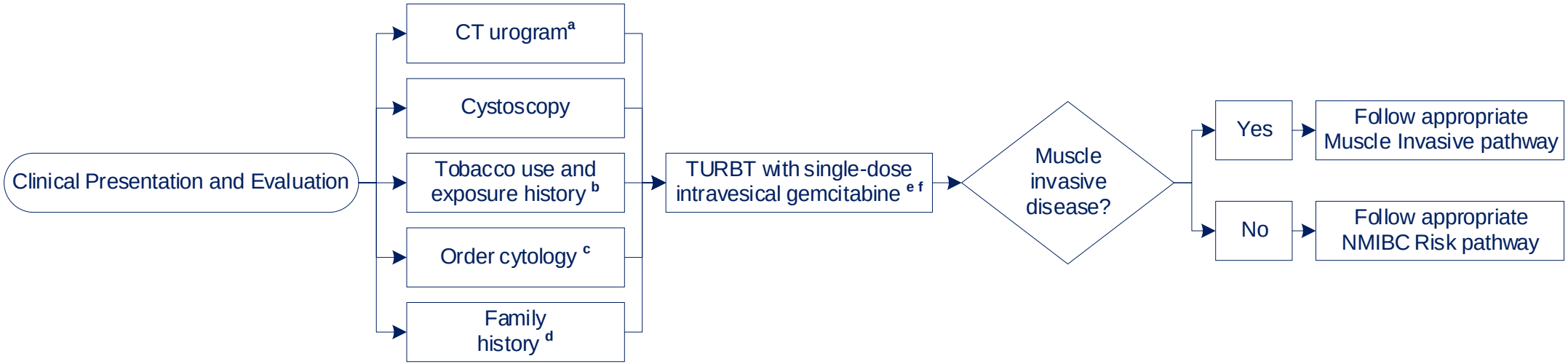
If the patient served on or after Sept. 11, 2001, in Afghanistan, Djibouti, Egypt, Jordan, Lebanon, Syria, Uzbekistan, or Yemen or if the patient served in the *Southwest Asia theater of operations, or Somalia, on or after Aug. 2, 1990, specific conditions include:

- Urinary bladder, ureter, and related genitourinary cancers

*The Southwest Asia theater of operations refers to Iraq, Kuwait, Saudi Arabia, the neutral zone between Iraq and Saudi Arabia, Bahrain, Qatar, the United Arab Emirates, Oman, the Gulf of Aden, the Gulf of Oman, the Persian Gulf, the Arabian Sea, the Red Sea, and the airspace above these locations.

For more information, please visit U.S. Department of Veterans Affairs - Presumptive Disability Benefits (va.gov); VA News - Presumptive for Service Connection Jan 08 2025; eCFR :: 38 CFR 3.320a -- Presumptive service connection for bladder, ureter, and related genitourinary cancers.

Bladder Cancer – Clinical Presentation and Evaluation



Clinical trial(s) always considered on pathway. For assistance finding a clinical trial, email CancerClinicalTrialsNavigation@va.gov.

[a] **CT Urogram** in patients unable to receive IV contrast, order alternative upper tract imaging

[b] **Exposure** includes Agent Orange, burn pits, and other occupational/environmental toxins

[c] **Cytology** order if results would change clinical management

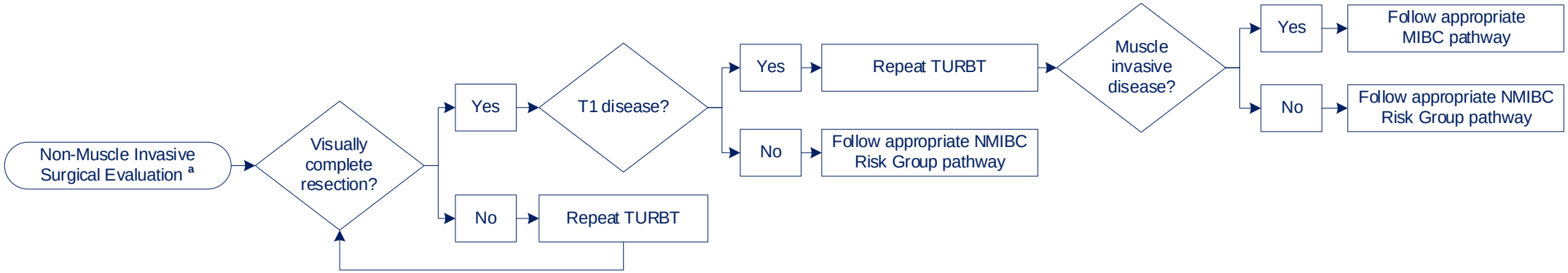
[d] **Family History** family or personal malignancy history, suspicion for Lynch syndrome, or age under 60 years

[e] **TURBT with EUA** include blue-light cystoscopy if clinically appropriate

[f] **Intravesical Gemcitabine** for known or presumed low grade

TURBT Transurethral Resection of Bladder Tumor
EUA Exam Under Anesthesia

Bladder Cancer – Non-Muscle Invasive Surgical Evaluation



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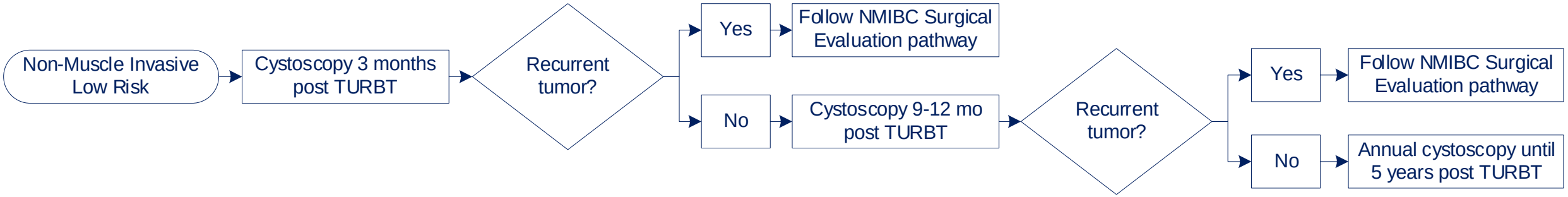
[a] **Variant Histology** includes micropapillary, nested, plasmacytoid, neuroendrocrine, sarcomatoid, squamous or glandular predominant

TURBT Transurethral Resection of Bladder Tumor

American Urological Association Non-Muscle Invasive Risk Stratification		
Low Risk	*Intermediate Risk*	*High Risk*
• Papillary urothelial neoplasm of low malignant potential *Or* • Low grade urothelial carcinoma ▪ Ta and ▪ ≤3 cm and ▪ Solitary	• Low grade urothelial carcinoma ▪ T1 or ▪ >3 cm or ▪ Multifocal or ▪ Recurrence within 1 year *Or* • High grade urothelial carcinoma ▪ Ta and ▪ <3 cm and ▪ Solitary	• High grade urothelial carcinoma ▪ CIS or ▪ T1 or ▪ >3 cm or ▪ Multifocal *Or* • Very high risk features (any) ▪ BCG unresponsive ▪ Variant histologies [a] ▪ Lymphovascular invasion ▪ Prostatic urethral involvement

Bladder Cancer – Non-Muscle Invasive Low Risk



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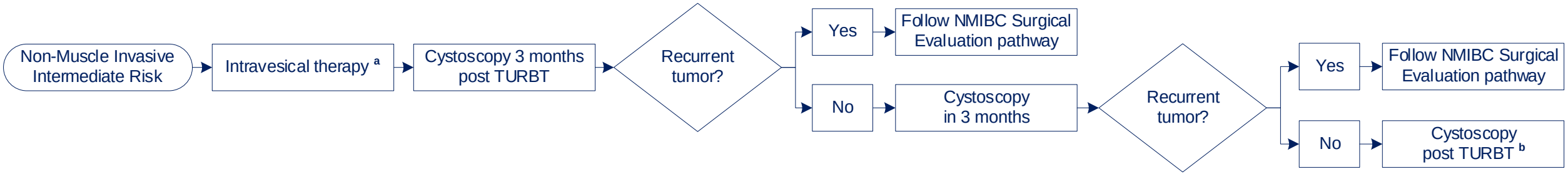
TURBT Transurethral Resection of Bladder Tumor

Bladder Cancer – Non-Muscle Invasive Intermediate Risk



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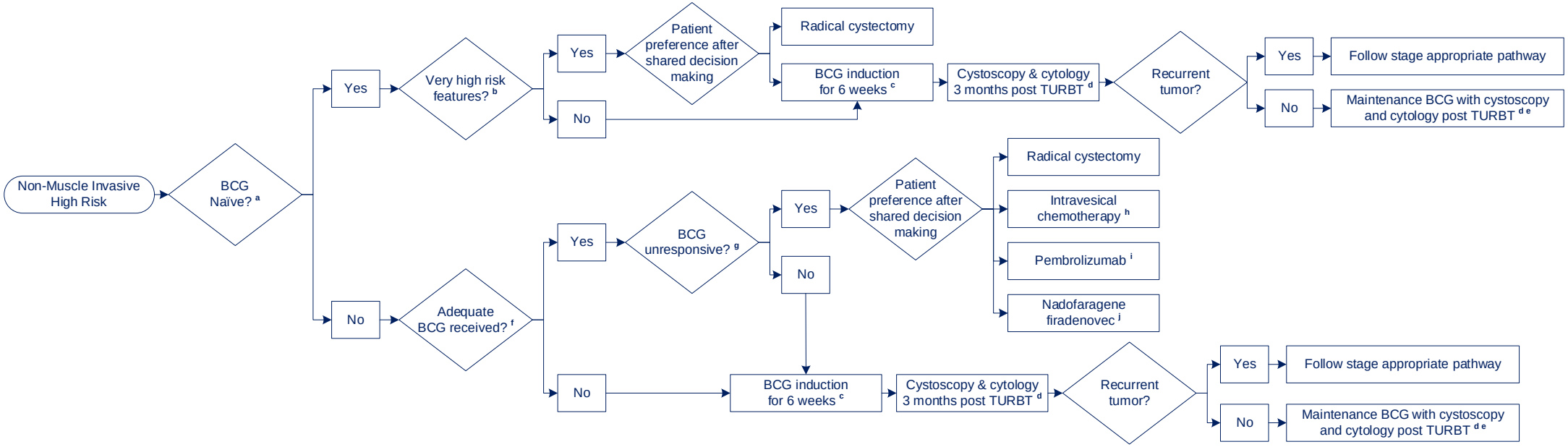
[a] **Intravesical Therapy** BCG weekly instillations for 6 weeks preferred for high grade disease; if low grade or not available, gemcitabine once a week for six weeks within 3-4 weeks of TURBT; BCG or gemcitabine maintenance should be continued for one year

[b] **Cystoscopy Post TURBT Schedule** at Year 1: at 3, 6, and 12 months; Year 2: every 6 months; Years 3 and later: annually

TURBT Transurethral Resection of Bladder Tumor

Bladder Cancer – Non-Muscle Invasive High Risk



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[a] **BCG Naïve** BCG non-exposed or greater than one year since last BCG

[b] **Very High Risk Features** include variant histologies, lymphovascular invasion, or prostatic urethral invasion

[c] **BCG Induction** only one repeat induction BCG course

[d] **Cystoscopy and Cytology Post TURBT** surveillance schedule: years 1-2: every 3 months; years 3-4: every 6 months; years ≥5: annually

[e] **BCG Maintenance** 3 week instillations at 3, 6, 12, 18, 24, 30, and 36 months (3 years) after start of induction BCG

[f] **Adequate BCG** defined as ≥5 induction doses and ≥2 maintenance doses

[g] **BCG Unresponsive** defined as persistent high-grade disease or recurrence within 6 months of receiving at least 2 courses of intravesical BCG (at least 5 of 6 induction and at least 2 of 3 maintenance doses of BCG)

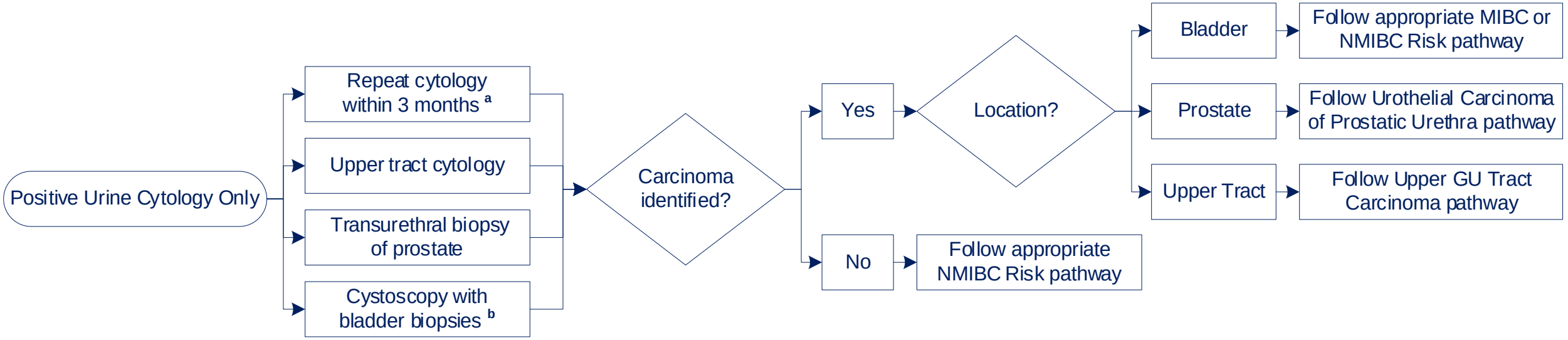
[h] **Intravesical Chemotherapy** gemcitabine and docetaxel preferred

[i] **Pembrolizumab** option for treatment of patients with BCG-unresponsive, high-risk NMIBC with Tis tumors who are ineligible for or have elected not to undergo cystectomy

[j] **Nadofaragene Firadenovec** all criteria must be met: BCG unresponsive, non-muscle invasive bladder cancer, ^1 Carcinoma in situ (CIS) with or without papillary tumors (Ta or T1 high-grade tumors)

BCG Bacillus Calmette Guerin
TURBT Transurethral Resection of Bladder Tumor

Bladder Cancer – Positive Urine Cytology Only



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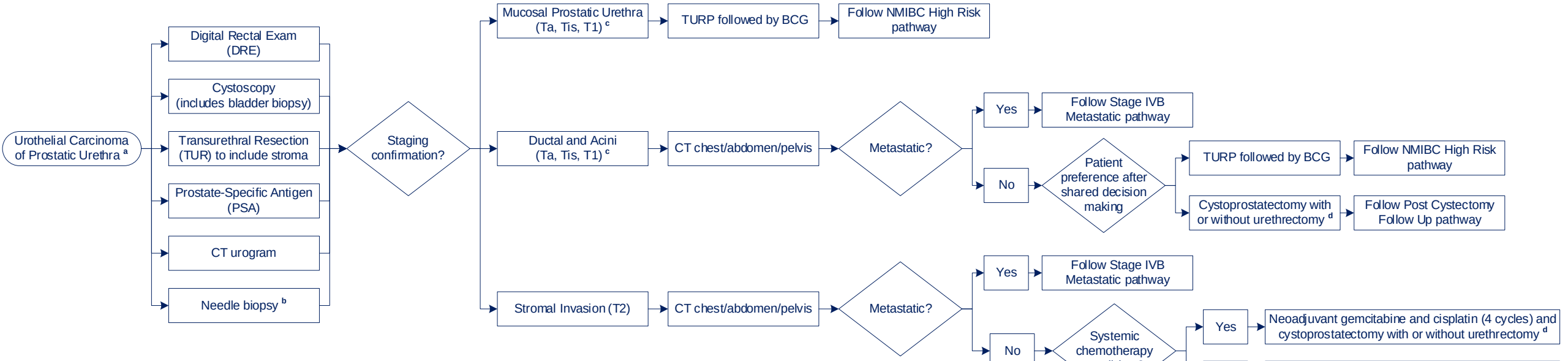
[a] **Cytology** review clinical history with cytopathologist

[b] **Cystoscopy** use enhanced technology if available

Bladder Cancer – Urothelial Carcinoma of Prostatic Urethra



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[a] **Urothelial Carcinoma of Prostatic Urethra** solely isolated prostatic urethra involvement

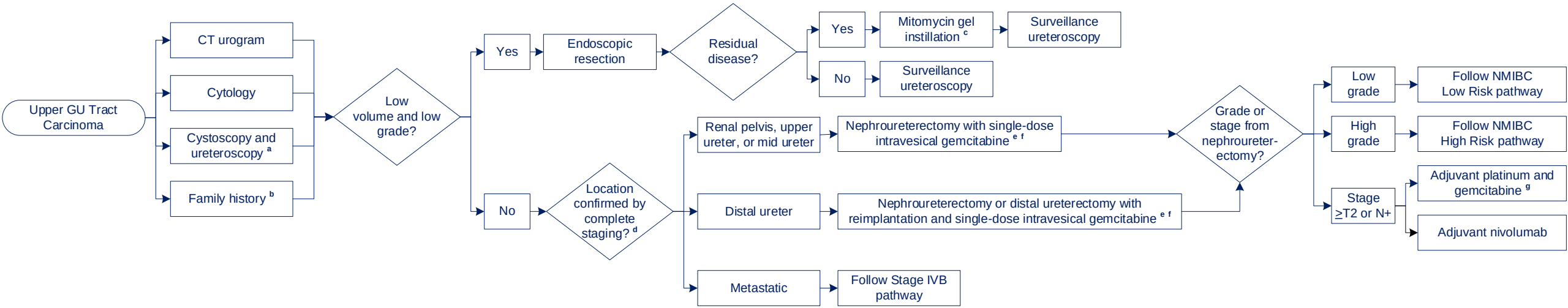
[b] **Needle Biopsy** if DRE or PSA is abnormal

[c] **Ta, Tis, T1** based on transurethral resection; confirm subepithelial involvement

[d] **If Only Prior Pelvic Metastatic Disease**, reimage with PET to ensure no metastatic disease prior to proceeding with surgery

TURP Transurethral Resection of the Prostate
BCG Bacillus Calmette-Guerin

Bladder Cancer – Upper GU Tract Carcinoma



Clinical trial(s) always considered on pathway. For assistance finding a clinical trial, email CancerClinicalTrialsNavigation@va.gov.

[a] **Cystoscopy and Ureteroscopy** may include selective washing ± single-dose intravesical gemcitabine

[b] **Family History** family or personal malignancy history, suspicion for Lynch syndrome; age under 60 years

[c] **Mitomycin Gel Instillation** use for ureteral tumors is off-label

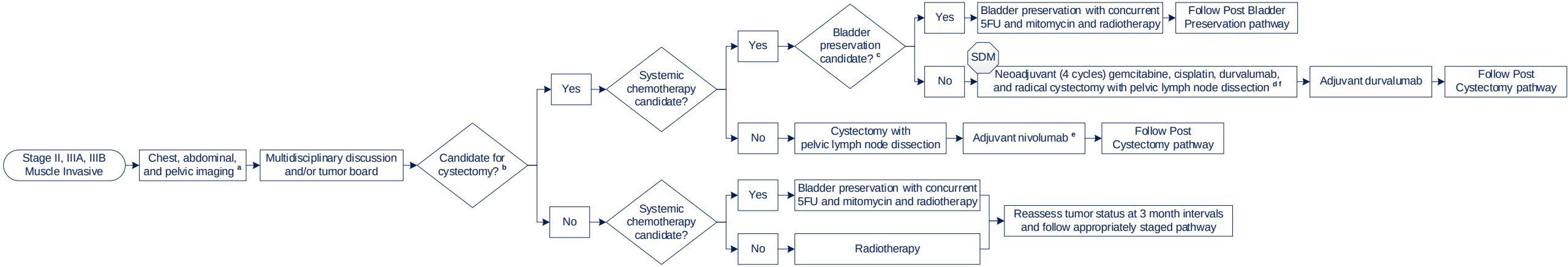
[d] **Complete Staging** to include recent chest and abdominal cross-sectional imaging

[e] **Consider Neoadjuvant Gemcitabine and Cisplatin** for select high grade patients; consider Tumor Board discussion

[f] **For High Grade** include regional lymphadenectomy

[g] **Adjuvant Therapy Options** include cisplatin if renal function allows and gemcitabine; carboplatin if not a cisplatin candidate and gemcitabine or nivolumab

Bladder Cancer – Stage II, IIIA, IIIB Muscle Invasive



Clinical trial(s) always considered on pathway. For assistance finding a clinical trial, email CancerClinicalTrialsNavigation@va.gov.

[a] **Imaging** perform bone scan if clinically indicated

[b] **Candidate for Cystectomy** patients with clinical node positive disease should have resolution of adenopathy post chemo to become eligible for cystectomy

[c] **Bladder Preservation** avoid bladder preservation in patients with hydronephrosis and extensive or multifocal carcinoma in situ

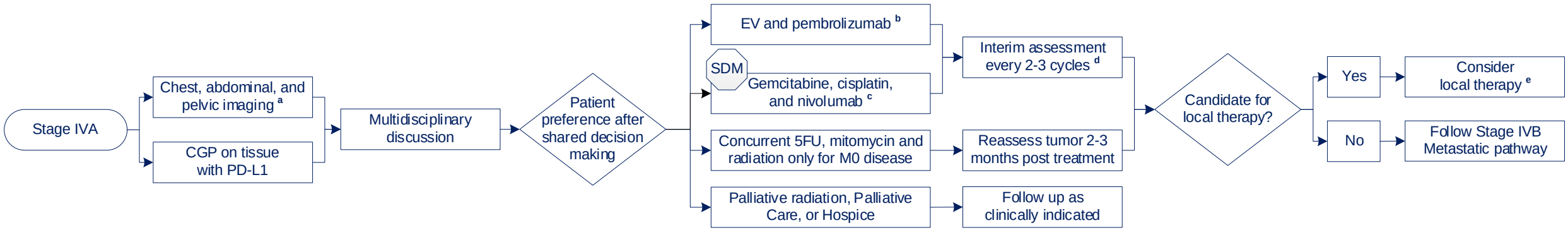
[d] **Platinum-Based Chemotherapy** dose-dense MVAC can be considered in select patients

[e] **Adjuvant Nivolumab** for patients with pT3, pT4a, or pN+ or ypT2 to ypT4a or ypN+ who received neoadjuvant cisplatin following radical cystectomy

[f] **SDM Durvalumab** shared decision making is critical at the time of consideration of durvalumab; in clinical trials, the control arm was chemotherapy alone and contained no information regarding any subsequent therapies in the control arm; thus, it is unclear if survival benefit is from neoadjuvant therapy alone, adjuvant therapy, or both components; physician should discuss these uncertainties with patients

MVAC Methotrexate, Vinblastine, Doxorubicin, Cisplatin

Bladder Cancer – Stage IVA



Clinical trial(s) always considered on pathway. For assistance finding a clinical trial, email CancerClinicalTrialsNavigation@va.gov.

[a] **Imaging** perform bone scan if clinically indicated

[b] **Eligible for EV** exclude patients with preexisting peripheral neuropathy ≥Grade 2, baseline ocular disorders, uncontrolled diabetes at baseline

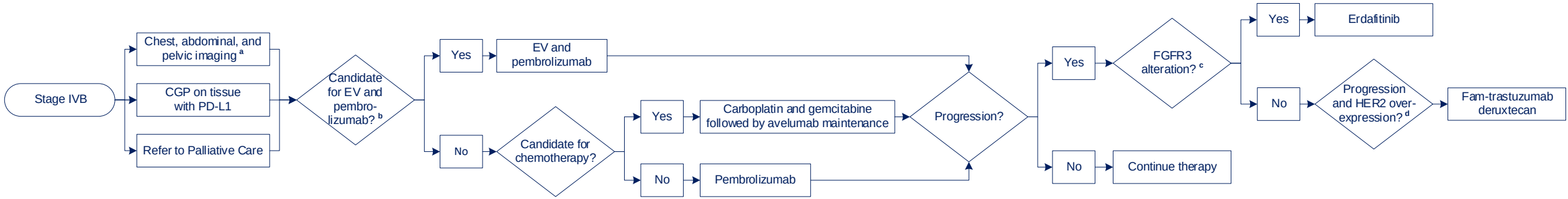
[c] **SDM Nivolumab** shared decision making is critical at the time of consideration of nivolumab; in the CheckMate 901 trial, only 40% of patients within the control arm received a checkpoint inhibitor as subsequent therapy; providers will need to assess cisplatin candidacy prior to using this regimen

[d] **Interim Assessment** includes EUA, cystoscopy, and CT chest/abdomen/pelvis

[e] **Local Therapy** may include radiation or cystectomy

CGP Comprehensive Genomic Profiling
EV Enfortumab Vedotin
EUA Exam Under Anesthesia

Bladder Cancer – Stage IVB



Clinical trial(s) always considered on pathway. For assistance finding a clinical trial, email CancerClinicalTrialsNavigation@va.gov.

[a] **Imaging** perform bone scan if clinically indicated, imaging of central nervous system (CNS) as clinically indicated

[b] **Candidate for EV** exclude patients with preexisting peripheral neuropathy ≥ Grade 2, baseline ocular disorders, uncontrolled diabetes at baseline

[c] **If Not a Candidate for These Therapies** consider hospice and/or palliative radiation

[d] **HER2** IHC3+ that progressed on previous therapy with no satisfactory alternative

CGP Comprehensive Genomic Profiling
EV Enfortumab Vedotin

Criteria for Use

Erdafitinib: exclude patients with retinal/corneal abnormality at baseline or serum phosphate greater than upper limits of normal at baseline; perform ophthalmological exams at baseline and then monthly for the first 4 months of therapy, then every 3 months thereafter

Enfortumab Vedotin: exclude patients with preexisting neuropathy ≥ Grade 2, baseline ocular disorders, or uncontrolled diabetes at baseline

Bladder Cancer – Post Cystectomy Follow Up

Post Cystectomy Follow Up

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 5-10	Year >10
Imaging NMIBC	CT urogram at 3 &12 mo	Annual CT urogram				Annual renal ultrasound	As clinically indicated
Imaging MIBC	CT chest and CT urogram every 3-6 mo		Annual CT chest/abdomen/pelvis			Annual renal ultrasound	As clinically indicated
Blood Tests	CMP &CBC every 6 mo	Annual CMP and B_{12} levels				Annual B_{12} levels	
Urine Tests	Urine cytology every 6-12 mo; consider urethral wash every 6-12 mo	Urine cytology as clinically indicated Urethral wash cytology as clinically indicated [a]					

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[a] **Urethral Wash** recommended for prostatic urethral involvement (papillary or CIS) on TURBT or cystectomy pathology

Bladder Cancer – Muscle Invasive Post Bladder Preservation Follow Up

Muscle Invasive
Post Bladder Preservation Follow Up

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 5-10	Year >10
Cystoscopy	Every 3 mo		Every 6 mo		Annually		As clinically indicated
Imaging	CT chest and CT urogram every 3-6 mo		Annual CT chest/abdomen/pelvis			As clinically indicated	
Blood Tests	CMP & CBC every 6 mo	Annual CMP					
Urine Tests	Urine cytology every 6-12 mo		Urine cytology as clinically indicated				

Bladder Cancer – Molecular Testing Table

Eligibility	Test Category	Test Type	Recommended Vendors	NPOP Coverage	Specimen Type
Stage IVA Muscle Invasive Urothelial Carcinoma/Bladder Cancer, Predominantly Urothelial	Somatic NGS	CGP using both DNA and RNA based methodology	Tempus Foundation Medicine	Yes Yes	Tumor Tissue*, Blood
	IHC	PD-L1 expression by IHC using 22C3 antibody (pembrolizumab), SP142 antibody (atezolizumab), 28-8 pharmDx antibody (nivolumab), SP263 antibody (durvalumab)	Tempus Foundation Medicine	Yes (When ordered with CGP) Yes (When ordered with CGP)	Tumor Tissue
Stage IVB Metastatic Urothelial Carcinoma/Bladder Cancer	Somatic NGS	CGP using both DNA and RNA based methodology	Tempus Foundation Medicine	Yes Yes	Tumor Tissue*, Blood
	IHC	PD-L1 expression by IHC using 22C3 antibody (pembrolizumab), SP142 antibody (atezolizumab), 28-8 pharmDx antibody (nivolumab), SP263 antibody (durvalumab)	Tempus Foundation Medicine	Yes (When ordered with CGP) Yes (When ordered with CGP)	Tumor Tissue
	IHC	HER2	Foundation Medicine	Yes (When ordered with CGP)	Tumor Tissue

* Tissue preferred, but liquid acceptable if tissue insufficient