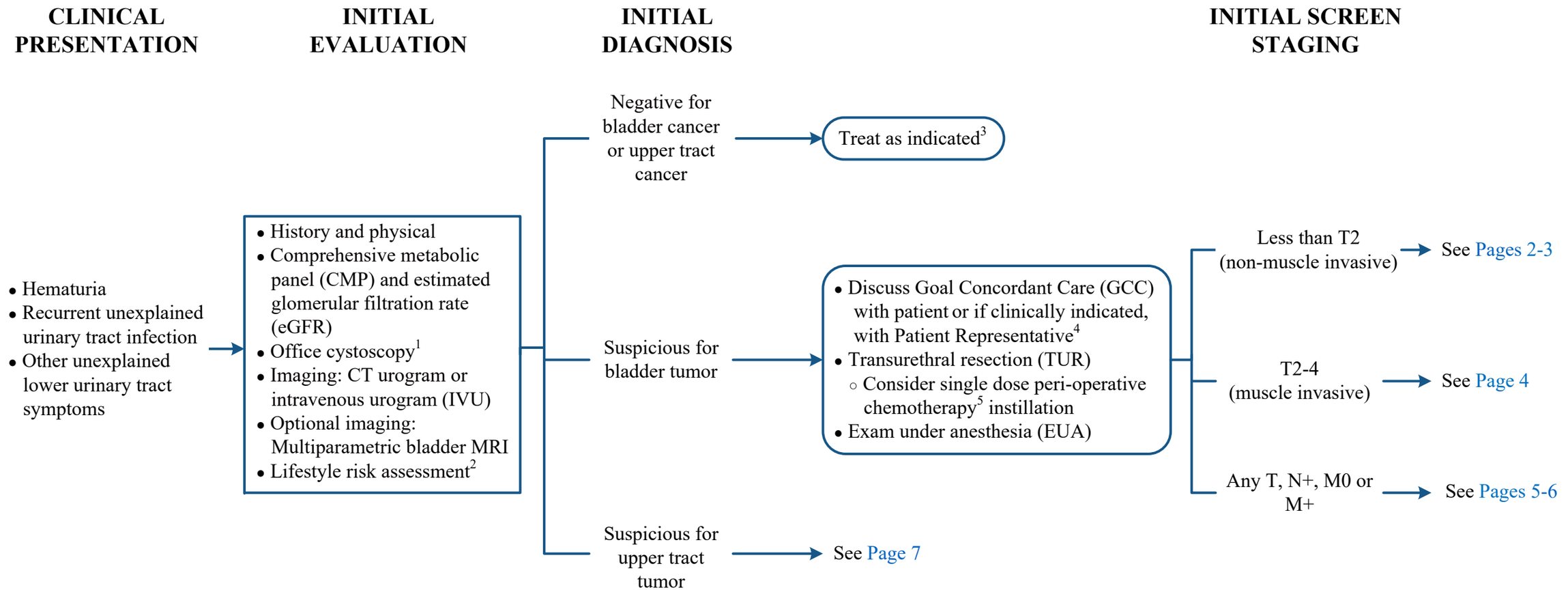
Urothelial Carcinoma of Bladder and Upper Tract

Note: Consider Clinical Trials as treatment options for eligible patients.



[1] May also consider urinary cytology or other MD Anderson approved genitourinary biomarkers

[2] See Physical Activity, Nutrition, Obesity Screening and Management, and Tobacco Cessation Treatment algorithms; ongoing reassessment of lifestyle risks should be a part of routine clinical practice

[3] If persistent microhematuria, recommend repeat of history and physical, office cystoscopy, imaging (CT urogram or IVU) in 2-3 years

[4] GCC should be initiated by the Primary Oncologist. If Primary Oncologist is unavailable, Primary Team/Attending Physician to initiate GCC discussion and notify Primary Oncologist. Patients or if clinically indicated the Patient Representative should be informed of therapeutic and/or palliative options. GCC discussion should be consistent, timely, and re-evaluated as clinically indicated. The Advance Care Planning (ACP) note should be used to document GCC discussion. Refer to the GCC home page (for internal use only).

[5] Refer to Principles of Intravesical Treatment on Page 11

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Urothelial Carcinoma of Bladder and Upper Tract

Note: Consider Clinical Trials as treatment options for eligible patients.

STAGE

TREATMENT AND FOLLOW-UP

Ta-Unifocal (low-grade solitary tumor) → TURBT and surveillance cystoscopy[1] at 3 months and if clear, then 9 months later (at 12 months after initial), and then annually → Recurrence?

- No → Surveillance cystoscopy[1] at 3 months and if clear, then 9 months later (at 12 months after initial), and then annually
- Yes →

Ta-Multifocal (low-grade) → BCG (weekly for 6 weeks) with or without maintenance **or**; Intravesical chemotherapy with maintenance for 1 year **or**; Active surveillance (in selected cases) **or**; Clinical trial → Repeat cystoscopy to assess response (with or without biopsy if indicated) at 3 months → Residual disease?

- Yes → Ta: Follow Ta - Multifocal path; Tis, T1-3: Follow appropriate path (Box A on current page for CIS, Box B on Page 3 for high grade Ta, Box C on Page 3 for T1 high risk, and Box D on Page 4 for T2-4 muscle invasive)
- No → Continue surveillance cystoscopy[1] (every 3 months for 2 years; every 6 months for 2 years; then annually)

A Carcinoma In-Situ (CIS) → BCG (weekly for 6 weeks) plus maintenance for 3 years → Cystoscopy[1] at 3 and 6 months → Persistent CIS at 6 months?

- Yes → Radical cystectomy **or**; Clinical trial **or**; Salvage intravesical therapy **or**; Nanoforging firadenovec **or**; Nogapendekin alfa inbakicep with BCG **or**; Pembrolizumab[2] → See Surveillance on Page 8
- No → Continue BCG as per SWOG protocol[3]; Continue surveillance cystoscopy[1] (every 3 months for 2 years; every 6 months for 2 years; then annually)

TURBT = transurethral resection of bladder tumor
BCG = Bacillus Calmette-Guerin
SWOG = Southwest Oncology Group

[1] Cystoscopy combined with either cytology or fluorescence in situ hybridization (FISH) cytology as indicated. In selected patients, fluorescent cystoscopy should be considered.

[2] Pembrolizumab is indicated for the treatment of patients with BCG–unresponsive, high-risk, non-muscle invasive bladder cancer (NMIBC) with carcinoma in situ (CIS) with or without papillary tumors who are ineligible for or have elected not to undergo cystectomy

[3] SWOG protocol includes BCG weekly for 6 weeks then 3 weekly maintenance at 3 months, 6 months, and every 6 months for 3 years total (27 instillations total)

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Urothelial Carcinoma of Bladder and Upper Tract

Note: Consider Clinical Trials as treatment options for eligible patients.

STAGE

TREATMENT AND FOLLOW-UP

B
High-Grade (HG) Ta or T1-Unifocal

Muscle in pathology specimen?

Yes → Consider repeating resection in 4-6 weeks, especially with T1

No →
- T1: re-biopsy to exclude T2
- Ta, HG: consider re-biopsy

cTa → BCG (weekly for 6 weeks) plus maintenance for 3 years → Cystoscopy; Consider repeat biopsy to assess response at 3 months (if positive cystoscopy or no initial TURBT) → Recurrent disease?

Yes →
- Radical cystectomy **or**
- Clinical trial **or**
- Nanoforging firadenovec **or**
- Nogapendekin alfa inbakicept with BCG **or**
- Pembrolizumab[1] **or**
- Gemcitabine with docetaxel

→ See Surveillance on Page 8

No →
- Continue BCG as per SWOG protocol[2]
- Continue surveillance cystoscopy[3] (every 3 months for 2 years; every 6 months for 2 years; then annually)

cT1 → Consider early cystectomy → Patient accepts surgery?

No → BCG (weekly for 6 weeks) plus maintenance for 3 years

Yes → Cystectomy → Upstaged at surgery?

Yes →
- pT3a → Observation
- pT3b → Consider adjuvant cisplatin **or** ifosfamide-based chemotherapy (see Page 12)
- N+, margins positive or prostatic stromal invasive pT4a → Consider adjuvant cisplatin **or** ifosfamide-based chemotherapy (see Page 12)

No → Observation

cT2 → See Page 4

C
High risk T1[4] → Consider early cystectomy

BCG = Bacillus Calmette-Guerin therapy
SWOG = Southwest Oncology Group

[1] Pembrolizumab is indicated for the treatment of patients with BCG-unresponsive, high-risk, non-muscle invasive bladder cancer (NMIBC) with carcinoma in situ (CIS) with or without papillary tumors who are ineligible for or have elected not to undergo cystectomy
[2] SWOG protocol includes BCG weekly for 6 weeks then 3 weekly maintenance at 3 months, 6 months and every 6 months for 3 years total (27 instillations total)
[3] Cystoscopy combined with either cytology or fluorescence in situ hybridization (FISH) cytology as indicated. In selected patients, fluorescent cystoscopy should be considered.
[4] T1 multifocal, variant histology with concurrent carcinoma in situ (CIS), lymphovascular invasion (LVI) and/or resectable tumor 3 cm or greater with poor prognosticator or too large to resect completely

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Urothelial Carcinoma of Bladder and Upper Tract

Note: Consider Clinical Trials as treatment options for eligible patients.

STAGE

TREATMENT AND FOLLOW-UP

D

T2-4 (muscle invasive)

- Examination under anesthesia (EUA)
- CT urogram protocol abdomen and pelvis with and without contrast
- CT chest with and without contrast
- Bone scan if elevated alkaline phosphatase, hypercalcemia, or bone pain

T2/3a, N0, M0

Presence of poor risk factors[1] and patient is suitable for systemic therapy?

Yes:
- Neoadjuvant chemotherapy[2]
- Clinical trial

→ Assess response by:
- Cystoscopy
- EUA
- Imaging

→ Resectable?

Yes → Radical cystectomy → See Surveillance on Page 8; See Box E if upstaged at surgery

No → Salvage therapy **or** consolidative radiation therapy → Consider cystectomy if surgically resectable

No:

Patient accepts surgery?

Yes → Cystectomy → **E** Upstaged at surgery[3]?

Yes:
- Adjuvant cisplatin **or** ifosfamide-based chemotherapy (see Page 12) if not received prior to surgery **or**
- Nivolumab if received chemotherapy prior to surgery
- Clinical trial

No → Observation

No → Bladder sparing treatment
- Chemoradiation **or**
- Clinical trial

T3b/4a, N0, M0

- Neoadjuvant chemotherapy[2]
- Clinical trial

T4b, N0, M0

Consider clinical trial if available

→ Assess response by:
- Cystoscopy
- EUA
- Imaging

→ Resectable?

Yes → Radical cystectomy → See Surveillance on Page 8; See Box E if upstaged at surgery

No → Additional chemotherapy **or** consolidative radiation therapy

MIBC = muscle invasive bladder cancer
NMIBC = non-muscle invasive bladder cancer

[1] Poor risk factors:
- Lymphovascular invasion
- Inability to assess depth of invasion
- Variant histology such as small cell
- Hydronephrosis
- Tumor involving bladder diverticulum
- Progression to MIBC from NMIBC after adequate BCG

[2] Consider neoadjuvant/adjuvant cisplatin or ifosfamide-based systemic chemotherapy (*i.e.,* DDMVAC, IAG, *etc.*). Refer to Principles of Systemic Therapy on Page 10

[3] Pathologic stage T3 or T4, N+, margins positive, or prostatic stromal invasion T4a

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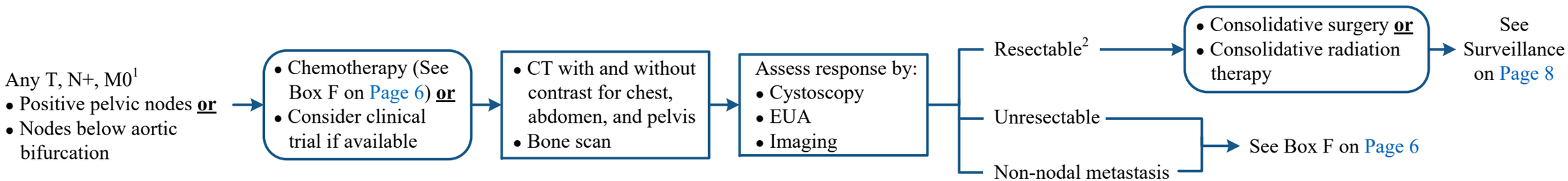
Urothelial Carcinoma of Bladder and Upper Tract

Note: Consider Clinical Trials as treatment options for eligible patients.

CLINICAL PRESENTATION

METASTATIC DISEASE



[1] Consider *FGFR* mutation testing and *HER2* IHC testing

[2] Patients are generally considered surgically resectable if no tumor present in the bladder and near complete response in lymph nodes. If tumor still present on cystoscopy or on biopsy of nodes, consider additional chemotherapy prior to considering surgical consolidation.

Urothelial Carcinoma of Bladder and Upper Tract

Note: Consider Clinical Trials as treatment options for eligible patients.

CLINICAL PRESENTATION

Any T, N+, M+[1]
- Nodes above aortic bifurcation **or**
- Visceral metastasis

→ CT with and without contrast for chest, abdomen, and pelvis
- Bone scan

→ **F**

TREATMENT

For patients with oligometastatic disease or oligoprogressive disease after upfront systemic therapy, metastasis directed therapy using consolidative radiation therapy should be considered. Clinical trial or systemic treatment[2] per patient's comorbidities:

Front-line systemic treatment:
- If no contraindication: enfortumab vedotin plus pembrolizumab
- If contraindication to enfortumab vedotin (*e.g.* biliary clearance issues) but eligible for cisplatin: nivolumab with gemcitabine and cisplatin
- If contraindication to immunotherapy (*e.g.* uncontrolled autoimmune disease): see regimens below
  - Cisplatin eligible:
    - CrCl ≥ 50 mL/minute: full dose cisplatin or ifosfamide-based combinations (*i.e.*, DDMVAC, GC, IAGem, ITP, GTP)
    - CrCl ≥ 40 mL/minute and < 50 mL/minute: modified cisplatin-combinations including DDMVAC with split-dose cisplatin, GC with split-dose cisplatin, CGI, or TMP
  - Cisplatin ineligible:
    - GCa, GTA, GCtx, GVinorelbine
    - Pembrolizumab for any patient ineligible for platinum-based chemotherapy
- Maintenance therapy with avelumab for patients with locally advanced or metastatic disease that has not progressed with first-line platinum containing chemotherapy

Second-line systemic treatment:
- *FGFR3* mutation or fusion: erdafitinib[3]
- *HER2* 3+ on IHC: fam-trastuzumab deruxtecan
- Wild type *FGFR3*:
  - Immune checkpoint inhibition: pembrolizumab, nivolumab, or avelumab
  - Ineligible for immune checkpoint inhibition: consider alternative chemotherapy regimen from the front-line list of therapies or single agent taxane or move to third-line treatment below

Third-line systemic treatment :
- Enfortumab vedotin (nectin-4 testing is not required)
- Ineligible for enfortumab vedotin: consider alternative chemotherapy regimen from front-line, erdafitinib[3] , or immune checkpoint inhibition if not previously received. Otherwise, move to fourth-line below.

Fourth-line systemic treatment:
- Sacituzumab govitecan (Trop-2 testing is not required)

DDMVAC = dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin
GC = gemcitabine and cisplatin
GCa = gemcitabine and carboplatin
IAGem = ifosfamide, doxorubicin, and gemcitabine
ITP = ifosfamide, paclitaxel, and cisplatin
GTP = gemcitabine, paclitaxel, and cisplatin
CGI = cisplatin, gemcitabine, and ifosfamide
TMP = paclitaxel, methotrexate, and cisplatin
GTA = gemcitabine, paclitaxel, and doxorubicin
GCtx = gemcitabine and cyclophosphamide
GVinorelbine = gemcitabine and vinorelbine
PD-L1 = programmed death-ligand 1
FGFR3 = fibroblast growth factor receptor 3

[1] Consider *FGFR* mutation testing and *HER2* IHC testing
[2] See Appendix A for standard systemic treatments
[3] Not on MD Anderson Formulary

Urothelial Carcinoma of Bladder and Upper Tract

Note: Consider Clinical Trials as treatment options for eligible patients.

CLINICAL PRESENTATION

Upper tract (renal pelvis or ureter) tumor

- Discuss GCC with patient[1] or if clinically indicated, with Patient Representative
- CT urogram
- Cystoscopy
- Ureteroscopy
- Biopsy (forceps or brush) strongly recommended
- Washing adequate only if positive for high grade
- MSI testing

TREATMENT AND FOLLOW-UP

Low risk[2]

Patient suitable for conservative management[3]?

- Yes → Consider instillation of mitomycin gel (Jelmyto™) **or**; Laser ablation **or**; Consider adjuvant instillation of BCG (2-3 weeks later) or intraluminal chemotherapy
- No → Surgical removal
  - Nephroureterectomy with bladder cuff
  - Occasionally may consider segmental resection
  - Regional node dissection (if high grade or stage)

Greater than or equal to pT3, LVI+, or N+, or based on expected recurrence risk per nomogram[4]?

- Yes → Consider adjuvant chemotherapy[5] **or** immunotherapy **or** clinical trials
- No → Observation

High risk: High grade disease, sessile architecture, cT3 on imaging, or based upon clinical nomograms[2]

Consider:
- Multidisciplinary discussion for neoadjuvant **or** adjuvant chemotherapy[5]
- Clinical trial

→ Surgical removal (as above)

Metastatic disease

See Box F on Page 6

MSI = microsatellite instability
LVI = lymphovascular invasion

[1] GCC should be initiated by the Primary Oncologist. If Primary Oncologist is unavailable, Primary Team/Attending Physician to initiate GCC discussion and notify Primary Oncologist. Patients or if clinically indicated the Patient Representative should be informed of therapeutic and/or palliative options. GCC discussion should be consistent, timely, and re-evaluated as clinically indicated. The Advance Care Planning (ACP) note should be used to document GCC discussion. Refer to the GCC home page (for internal use only).

[2] See Appendix B, Appendix C, and Appendix D for clinical risk nomograms

[3] Conservative management is based on individual patient status and clinical findings; elective indications ideally meet low-risk European Association of Urology (EAU) criteria: unifocal disease, tumor size < 2 cm, low-grade cytology, low-grade ureteroscopic (URS) biopsy, and no invasive aspect on computed tomography urography (CTU)

[4] Refer to postoperative nomogram for prediction of relapse-free survival

[5] Consider neoadjuvant/adjuvant cisplatin or ifosfamide-based systemic chemotherapy (*i.e.*, DDMVAC, IAG, *etc.*). Refer to Principles of Systemic Therapy on Page 10.

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Urothelial Carcinoma of Bladder and Upper Tract

Note: Consider Clinical Trials as treatment options for eligible patients.

SURVEILLANCE AFTER RADICAL CYSTECTOMY

	Month								
	3	**6**	**12**	**18**	**24**	**30**	**36**	**48**	**60 or more**
Less than or equal to pT1 (no variant histology)[1]									Refer to Survivorship – Bladder/Ureter/ Renal Pelvis Cancer algorithm
History[2] / PE / Laboratory[3]	x	x	x		x		x	x	
Chest X-ray			x		x		x	x	
CT urogram	x	x		x		x	x	x	
CT abdomen and pelvis		x[4]							
pT2 N0:									
History[2] / PE / Laboratory[3]	x	x	x	x	x	x	x	x	
Chest X-ray		x	x	x	x	x	x	x	
CT urogram			x		x		x	x	
CT abdomen and pelvis		x		x					
pT3/T4 or pTxN+:									
History[2] / PE / Laboratory[3]	x	x	x	x	x	x	x	x	
Chest X-ray	x	x	x	x	x	x	x	x	
CT urogram			x		x		x	x	
CT abdomen and pelvis	x	x		x		x			

PE = physical examination

[1] Patients with adverse pathologic features, e.g. micropapillary disease, presence of lymphovascular invasion (LVI), sacromatoid de-differentiation, or those who have been downstaged after neoadjuvant chemotherapy, may be followed as pT2 patients
[2] History should include urethral discharge/bloody mucus
[3] Laboratory tests include CBC, electrolytes, BUN, creatinine, and LFTs. Cytology is optional if imaging is routinely obtained.
[4] As clinically indicated

Note: For all patients with urinary diversion, imaging study 6-8 weeks after surgery to confirm patency of anastomosis is at treating surgeon's discretion. Choices include: loopogram (or cystogram), IVU, or renal ultrasound.

Note: Consider Clinical Trials as treatment options for eligible patients.

BLADDER CANCER TREATMENT PRINCIPLES

PRINCIPLES OF RADIATION THERAPY MANAGEMENT OF INVASIVE DISEASE

- External beam radiation is rarely appropriate for patients with superficial tumors or carcinoma in situ (CIS). Surgery remains the standard of care.
- Precede radiation by maximal transurethral resection of the bladder tumor (TURBT) when safely possible
- Combining concurrent chemotherapy with radiation is encouraged for added tumor cytotoxicity
- Simulate and treat patients with the bladder empty
- Use multiple fields from high-energy linear accelerator beams
- Treat the whole bladder with 40-55 Gy and then boost bladder tumor to a total dose of 64-66 Gy excluding, if possible, normal areas of bladder from the high-dose volume
- TURBT followed by chemoradiation is an option for patients with non-muscle invasive bladder cancer refractory to BCG with limited phase II data
- Precede radiation by maximally safe transurethral resection of bladder tumor (TURBT)
- Combining concurrent chemotherapy with radiation is standard of care. Radiosensitizing chemotherapy can include weekly cisplatin, once or biweekly gemcitabine. For patients not candidates for concurrent chemotherapy, concurrent immunotherapy such as pembrolizumab can be used.
- Radiation planning will use optimal bladder filling in order to reduce bowel dose and spare normal bladder in select cases. This may include both full and empty bladder filling at time of radiation simulation or only empty bladder.
- Radiation technique will include IMRT/VMAT (intensity modulated radiation/volumetric arc therapy) as standard of care
- Dose and fractionation regimens include 55 Gy in 20 fractions over 4 weeks or 64 Gy in 32 fractions over 6.5 weeks
- Radiation to the surrounding pelvic lymph nodes are recommended for patients with large T2 tumors, T3-T4 tumors, variant subtypes, and those with node positive disease
- For patients with node positive disease, radiation to the bladder and surrounding lymph nodes with nodal boost is recommended without violation of bowel dose constraints

Continued on next page

Note: Consider Clinical Trials as treatment options for eligible patients.

BLADDER CANCER TREATMENT PRINCIPLES - continued

PRINCIPLES OF SYSTEMIC THERAPY

- Enfortumab vedotin plus pembrolizumab is a frontline combination for treatment of metastatic disease
- An alternative frontline regimen is gemcitabine, cisplatin plus nivolumab
- Two-to-three drug combinations based on cisplatin, docetaxel, paclitaxel, ifosfamide, gemcitabine or MVAC (methotrexate, vinblastine, doxorubicin, cisplatin) may still be used for treatment of metastatic disease in those ineligible for immunotherapy. Adjuvant or neoadjuvant therapy is also considered for patients at high risk of recurrence. Adjuvant immunotherapy can be considered for those not suitable for adjuvant chemotherapy.
- Patients at increased risk for morbidity from more toxic regimens (*e.g.*, MVAC) may be treated with combinations of lower toxicity profiles. These patients are characterized by more than one of the following:
  - Comorbid conditions
  - Poor performance status
  - Liver or bone metastases
  - High alkaline phosphatase
  - High lactate dehydrogenase
  - Poor renal function
- Pembrolizumab is indicated for front-line platinum ineligible patients
- Immunotherapy (pembrolizumab, nivolumab, or avelumab) has been approved for patients failing frontline chemotherapy. *PD-L1* testing is not required.
- Erdafitinib has been approved second-line for patients with *FGFR3* mutations and fusions
- Enfortumab vedotin has been approved for third-line setting. Nectin-4 testing is not required.
- Fam-trastuzumab deruxtecan has been approved subsequent line therapy for patients with *HER2* 3+ on IHC
- Sacituzumab govitecan is indicated for the 4th line treatment of metastatic urothelial cancer. Trop-2 testing is not required.

Continued on next page

Note: Consider Clinical Trials as treatment options for eligible patients.

BLADDER CANCER TREATMENT PRINCIPLES - continued

PRINCIPLES OF SURGICAL MANAGEMENT

- Transurethral resection of bladder tumor (TURBT)
  - The first step in surgical management of bladder tumors is a complete TURBT. Muscle must be present in the TURBT specimen to appropriately stage the tumor; if no muscle is present in the specimen, re-resection/biopsy of tumor base should be discussed with patient.
  - Repeat TURBT at 4-6 weeks is to be strongly considered if incomplete initial resection, no muscle in specimen, or T1 stage. It must also be considered if first TURBT does not allow adequate staging or attribution of risk factor for treatment selection or when using bladder-preserving treatment by chemotherapy and/or radiation therapy.
  - In cases of positive cytology with no evidence of tumor, patient should undergo multiple biopsies of the bladder mucosa (if visibly abnormal with or without use of fluorescent cystoscopy) as well as prostate urethral biopsies and evaluation of upper tracts
- Radical cystectomy
  - Radical cystectomy should include bilateral pelvic node resection with goal of at least 10 nodes removed
  - Nerve sparing and type of diversion selected depends on many factors, several of which are patient specific

PRINCIPLES OF INTRAVESICAL TREATMENT

- Immunotherapy
  - Bacillus Calmette-Guerin (BCG) immunotherapy is the most effective treatment for non-muscle invasive bladder cancer
  - It is ideal to wait 14-21 days after TURBT (no gross hematuria)
  - BCG induction (6 weekly treatments) should be followed by maintenance therapy (weekly for 3 weeks at months 3 and 6, and then every 6 months for a total of 3 years)
  - Dose reduction of BCG is preferable to shorter duration of maintenance
  - If patient fails 2 courses of BCG, strongly consider radical cystectomy or clinical trial
- Chemotherapy
  - Peri-operative intravesical chemotherapy is most effective when given right after TURBT (ideally within 6 hours)
  - Induction and maintenance chemotherapy in selected patients if indicated
  - Agents include gemcitabine and mitomycin
- Salvage therapy after BCG is preferably with combination chemotherapy (*i.e.*, gemcitabine and docetaxel)

Urothelial Carcinoma of Bladder and Upper Tract

APPENDIX A: Standard Systemic Treatments

Chemotherapy Regimens:

- Dose-dense MVAC (DDMVAC):
  Methotrexate 30 mg/m^2 IV **and**
  Vinblastine 3 mg/m^2 IV **and**
  Doxorubicin 30 mg/m^2 IV **and**
  Cisplatin 70 mg/m^2 IV
  - Cisplatin followed with ½ NS IV plus mannitol 40 g/L typically for 3 Liters

  This regimen is repeated every 2 weeks with growth factor support

- Gemcitabine, Cisplatin (GC):
  Gemcitabine 900 mg/m^2 IV over 90 minutes[a] on Day 1 and Day 8 **and**
  Cisplatin 70 mg/m^2 IV on Day 1
  - Cisplatin followed with ½ NS IV plus mannitol 40 g/L typically for 3 Liters

  This regimen is repeated every 3 weeks with growth factor support

- Gemcitabine, Carboplatin (GCa):
  Gemcitabine 900 mg/m^2 IV over 90 minutes[a] on Day 1 and Day 8 **and**
  Carboplatin AUC 4.5 IV on Day 1

  This regimen is repeated every 3 weeks with growth factor support

- Gemcitabine, Paclitaxel, Doxorubicin (GTA):
  Doxorubicin 30 mg/m^2 IV **and**
  Paclitaxel 135 mg/m^2 IV **and**
  Gemcitabine 900 mg/m^2 IV over 90 minutes[a]

  This regimen is repeated every 2 weeks with growth factor support

- Ifosfamide, Doxorubicin, Gemcitabine (IAGem):
  Ifosfamide 1,500 mg/m^2 IV plus mesna 300 mg/m^2 IV on Day 1 through Day 4 **and**
  - Mesna given at hours 0, 4, and 8 (with respect to ifosfamide's start time)

  Doxorubicin 45 mg/m^2 IV on Day 3 only **and**
  Gemcitabine 150 mg/m^2 IV over 30 minutes on Day 2 and Day 4

  This regimen is repeated every 3 weeks with growth factor support

- Cisplatin, Gemcitabine, Ifosfamide (CGI):
  Gemcitabine 900 mg/m^2 IV over 90 minutes[a] **and**
  Ifosfamide 1,000 mg/m^2 IV **and**
  Cisplatin 50 mg/m^2 IV on Day 1
  - Cisplatin followed with ½ NS IV plus mannitol 40 g/L, typically for 3 Liters

  This regimen is repeated every 2 weeks with growth factor support

- Paclitaxel, Methotrexate, Cisplatin (TMP):
  Methotrexate 30 mg/m^2 IV **and**
  Paclitaxel 100 mg/m^2 IV **and**
  Cisplatin 40 mg/m^2 IV
  - Cisplatin followed with ½ NS IV plus mannitol 40 g/L, typically for 3 Liters

  This regimen is repeated every 2 weeks with growth factor support

- Gemcitabine, Vinorelbine (GemVinorelbine):
  Vinorelbine 25 mg/m^2 IV **and**
  Gemcitabine 900 mg/m^2 IV over 90 minutes[a]

  This regimen is repeated every 2 weeks with growth factor support

[a] Fixed dose rate of 10 mg/m^2/minute. Infusion duration changes according to dose.

Continued on next page

APPENDIX A: Standard Systemic Treatments - continued

Chemotherapy Regimens (*continued*):

- Ifosfamide, Paclitaxel, Cisplatin (ITP):
  Paclitaxel 200 mg/m^2 IV **and**
  Ifosfamide 1,500 mg/m^2 plus mesna 300 mg/m^2 IV on Day 1 through Day 3 **and**
  - Mesna given at hours 0, 4, and 8 (with respect to ifosfamide's start time)

  Cisplatin 70 mg/m^2 IV
  - Cisplatin followed with ½ NS IV plus mannitol 40 g/L, typically for 3 Liters

This regimen is repeated every 3 weeks with growth factor support

- Gemcitabine, Paclitaxel, Cisplatin (GTP):
  Paclitaxel 80 mg/m^2 IV on Day 1 and Day 8 **and**
  Gemcitabine 900 mg/m^2 IV over 90 minutes[a] on Day 1 and Day 8 **and**
  Cisplatin 70 mg/m^2 IV on Day 1
  - Cisplatin followed with ½ NS IV plus mannitol 40 g/L, typically for 3 Liters

This regimen is repeated every 3 weeks with growth factor support

Immunotherapy:

- Avelumab 800 mg IV every 2 weeks
- Nivolumab 240 mg IV every 2 weeks or 480 mg IV every 4 weeks
- Nivolumab 360 mg IV on Day 1 with gemcitabine and cisplatin (GC) every 3 weeks for 6 cycles, followed by nivolumab 480 mg IV every 4 weeks
- Pembrolizumab 200 mg IV every 3 weeks or 400 mg IV every 6 weeks

Antibody Drug Conjugate:

- Enfortumab vedotin 1.25 mg/kg (maximum dose 125 mg) IV on Days 1, 8, and 15 of a 4-week cycle
- Enfortumab vedotin 1.25 mg/kg (maximum dose 125 mg) IV on Days 1 and 8, with pembrolizumab 200 mg IV on Day 1, of a 3-week cycle
- Fam-trastuzumab deruxtecan 5.4 mg/kg IV every 3 weeks
- Sacituzumab govitecan 10 mg/kg IV on Day 1 and Day 8 of a 3-week cycle

Targeted Therapy:

- Erdafitinib[b] 8 mg PO daily
  - May titrate up to 9 mg PO daily if phosphorous level on Day 14 to 21 is < 9 mg/dL

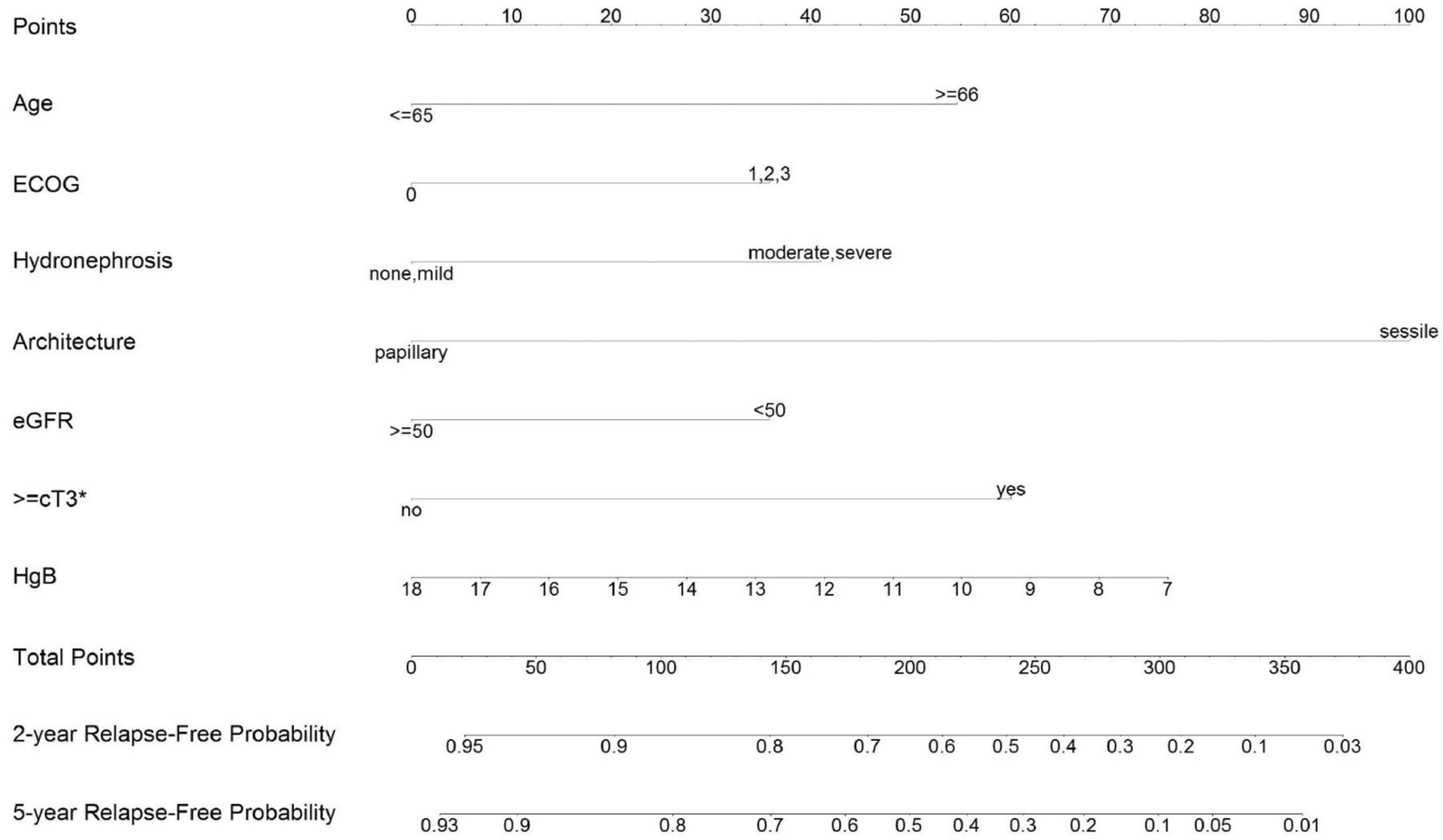
[a] Fixed dose rate of 10 mg/m^2/minute. Infusion duration changes according to dose

[b] Not on MD Anderson Formulary

Urothelial Carcinoma of Bladder and Upper Tract

APPENDIX B: Clinical Risk Nomograms

Preoperative relapse-free probability following radical nephroureterectomy for high grade upper tract urothelial carcinoma

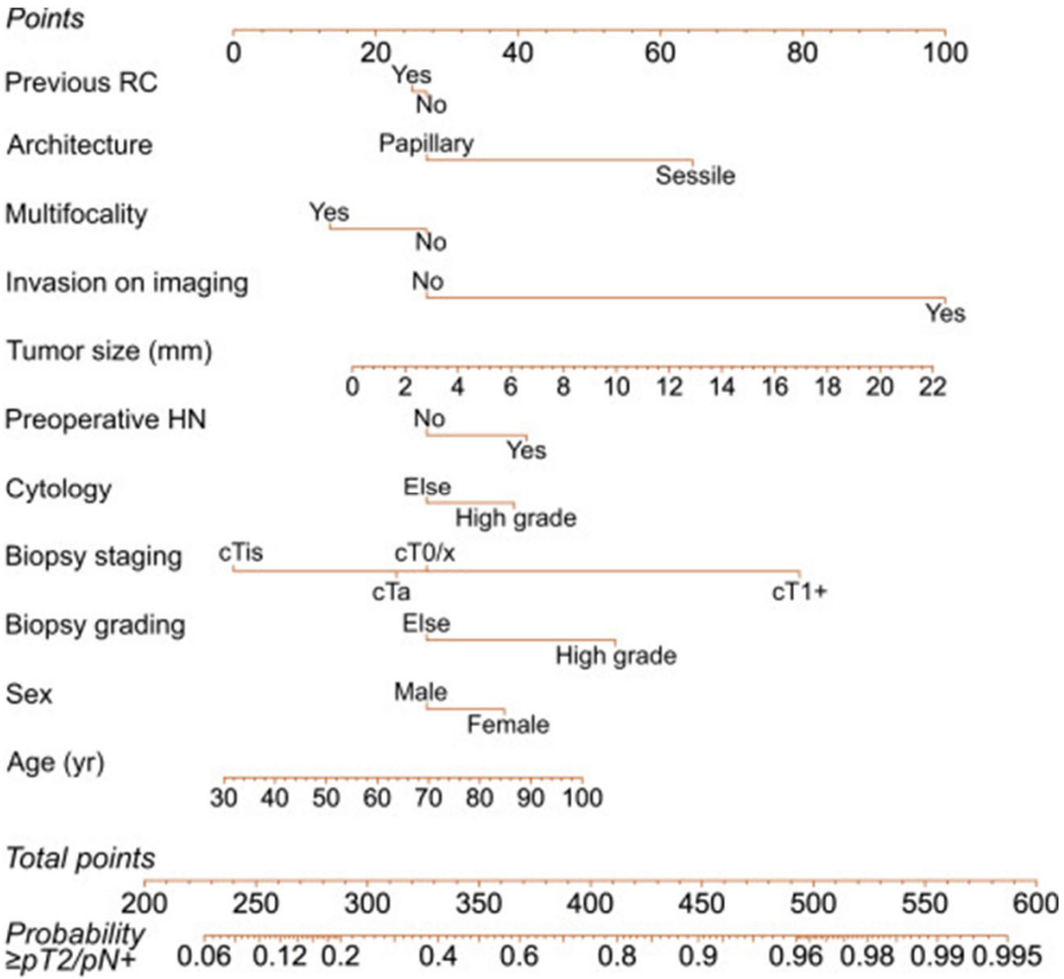


* based on imaging studies

From "Preoperative predictive model and nomogram for disease recurrence following radical nephroureterectomy for high grade upper tract urothelial carcinoma," by Y. Freifeld, R. Ghandour, N. Singla, S. Woldu, T. Clinton, … V. Margulis, 2019, *Urologic Oncology: Seminars and Original Investigations, 37*, p. 763. Copyright 2019 by Elsevier Inc. Reprinted with permission.

APPENDIX C: Clinical Risk Nomograms

Predicting the probability of ≥pT2/pN+ disease in patients undergoing radical nephroureterectomy



Instructions: Locate the patient's age on the corresponding axis. Draw a line straight upward to the point axis to determine the points toward the probability of ≥pT2/pN+ disease the patient receives for his age value. Perform this process for each additional variable and sum the points for each predictor. Locate the final sum on the total point axis. Draw a line straight down to find the patient's probability of having ≥pT2/pN+ disease. HN = hydronephrosis; RC = radical cystectomy.

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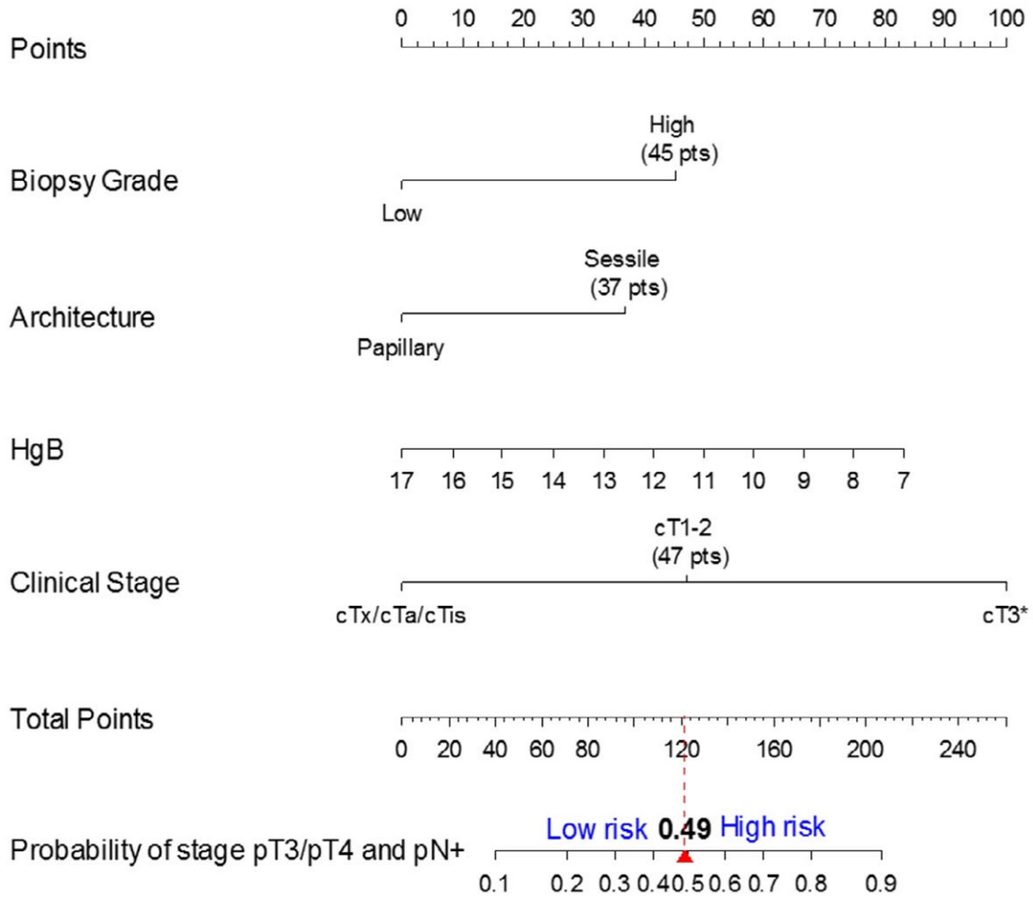
APPENDIX D: Clinical Risk Nomograms

Preoperative probability of non-organ confined (pT3-4, N+) upper tract urothelial carcinoma, low or high grade



* Peripelvic fat, parenchymal invasion (renal tumor) or periureteral fat invasion (ureteral tumor) or other infiltrative component on imaging

From "Preoperative multiplex nomogram for prediction of high-risk nonorgan-confined upper-tract urothelial carcinoma," by F. G. Petros, W. Qiao, N. Singla, T. N. Clinton, H. Robyak, J. D. Raman, . . . S. F. Matin, 2019, *Urologic Oncology: Seminars and Original Investigations, 37(4)*, p. 292.e6. Copyright 2018 by Elsevier Inc. Reprinted with permission.

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Other Supportive Readings

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MD Anderson Institutional Policy #CLN1202 - Advance Care Planning Policy. Advance Care Planning (ACP) Conversation Workflow (ATT1925)

Panebianco, V., Narumi, Y., Altun, E., Bochner, B. H., Efstathiou, J. A., Hafeez, S., … Catto, J. W. (2018). Multiparametric magnetic resonance imaging for bladder cancer: Development of VI-RADS (vesical imaging-reporting and data system). *European Urology*, *74*(3), 294-306. doi:10.1016/j.eururo.2018.04.029

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DEVELOPMENT CREDITS

This practice algorithm is based on majority expert opinion of the Genitourinary Center providers at the University of Texas MD Anderson Cancer Center. It was developed using a multidisciplinary approach that included input from the following:

Core Development Team Leads

Omar Alhalabi, MD (Genitourinary Medical Oncology)
Comron Hassanzadeh, MD (Genitourinary Radiation Oncology)
Ashish Kamat, MD (Urology)
Arlene Siefker-Radtke, MD (Genitourinary Medical Oncology)

Workgroup Members

John C. Araujo, MD, PhD (Genitourinary Medical Oncology)
Kelly Bree, MD (Urology)
Matthew Campbell, MD (Genitourinary Medical Oncology)
Henry Cao, PharmD (Pharmacy Clinical Programs)
Seungtaek L. Choi, MD (Genitourinary Radiation Oncology)
Paul Corn, MD, PhD (Genitourinary Medical Oncology)
Monica Desai, MD (Genitourinary Medical Oncology)
Colin P. Dinney, MD (Urology)
Olga N. Fleckenstein, BS♦
Jianjun Gao, MD, PhD (Genitourinary Medical Oncology)
Sangeeta Goswami, MD, PhD (Genitourinary Medical Oncology)
Eric Jonasch, MD (Genitourinary Medical Oncology)
Craig Kovitz, MD (Genitourinary Medical Oncology)
Byron Lee, MD, PhD (Urology)
Christopher J. Logothetis, MD (Genitourinary Medical Oncology)
Surena Matin, MD (Urology)
Neema Navai, MD (Urology)
Chaan S. Ng, MD (Abdominal Imaging)
Van Nguyen, PharmD♦
Amy Pai, PharmD♦
John Papadopoulos, MD (Urology)
Curtis A. Pettaway, MD (Urology)
Louis L. Pisters, MD (Urology)
Amishi Shah, MD (Genitourinary Medical Oncology)
Padmanee Sharma, MD, PhD (Genitourinary Medical Oncology)
Aradhana Venkatesan, MD (Radiology)
Raghu Vikram, MD (Abdominal Imaging)
Jianbo Wang, MD, PhD (Genitourinary Medical Oncology)
Run Wang, MD (Urology)
Ouida Lenaine Westney, MD (Urology)
Amado Zurita-Saavedra, MD (Genitourinary Medical Oncology)

♦Clinical Effectiveness Development Team