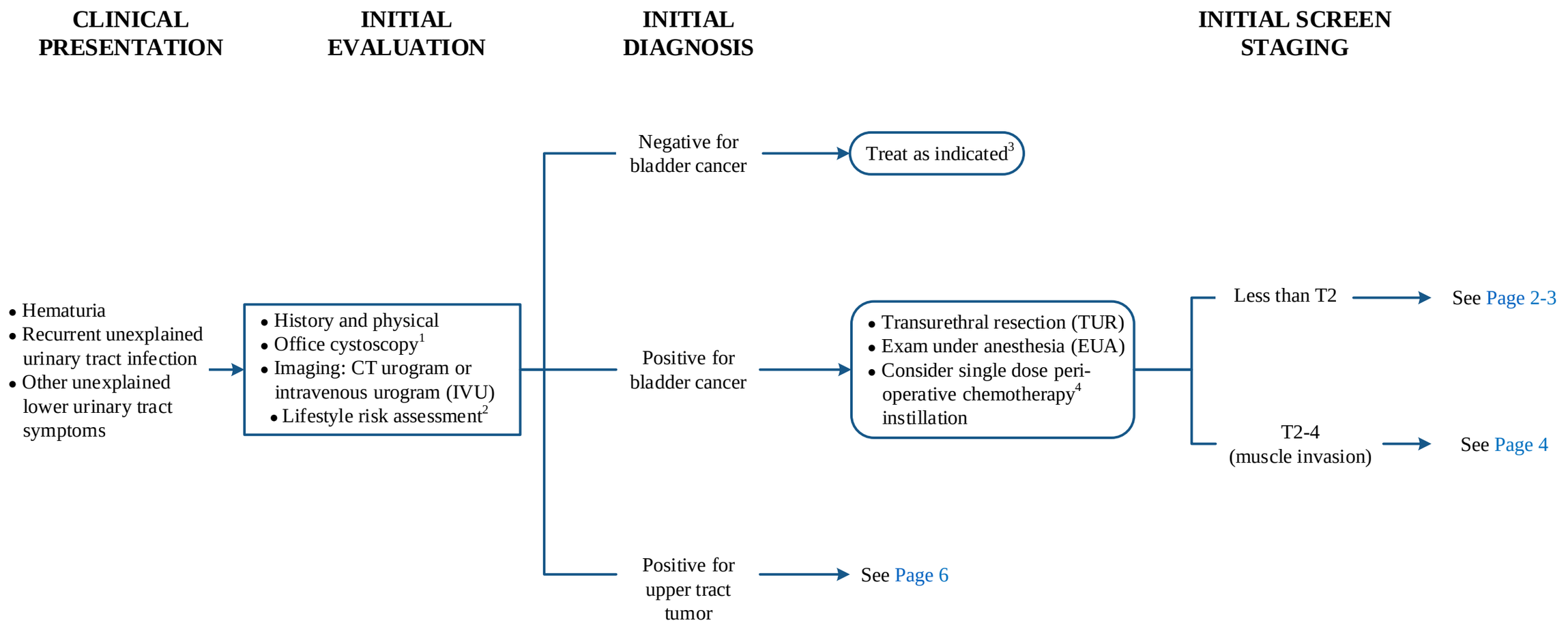
Urothelial Carcinoma of Bladder and Upper Tract

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



[1] Consider urinary cytology or other MD Anderson approved genitourinary biomarkers
[2] See Physical Activity, Nutrition, and Tobacco Cessation algorithms; ongoing reassessment of lifestyle risks should be a part of routine clinical practice
[3] If persistant microhematuria, recommend repeat of history and physical, office cystoscopy, imaging (CT urogram or IVU) in 2-3 years
[4] Refer to Principles of Intravesical Treatment on Page 8

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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) → TUR and surveillance cystoscopy[1] at 3 months and if clear, then 9 months later (at 12 months after initial), and then annually → Recurrence?
- No → (back to TUR and surveillance cystoscopy[1])
- Yes → (proceed)

Ta-Multifocal (low-grade) →
- BCG (weekly for 6 weeks) with or without maintenance **or**
- Intravesical chemotherapy with maintenance for 1 year **or**
- Observation (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
- No → Continue surveillance cystoscopy[1] (every 3 months for 2 years; every 6 months for 2 years; then annually)

Carcinoma In-Situ (CIS) → BCG (weekly for 6 weeks) plus maintenance for 3 years → Cystoscopy[1] at 3 and 6 months → Persistent carcinoma in-situ at 6 months?
- Yes →
  - Radical cystectomy **or**
  - Clinical trial **or**
  - Salvage intravesical therapy **or**
  - Pembrolizumab[2]

  → See Surveillance on Page 7
- No →
  - Continue BCG as per SWOG protocol
  - Continue surveillance cystoscopy[1] (every 3 months for 2 years; every 6 months for 2 years; then annually)

BCG = Bacillus Calmette-Guerin therapy
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

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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

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 TUR) → Residual disease?

Yes → • Radical cystectomy **or**
• Clinical trial **or**
• Pembrolizumab[1] → See Surveillance on Page 7

No → • Continue BCG as per SWOG protocol
• Continue surveillance cystoscopy[2] (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 9)

N+, margins positive or prostatic stromal invasion pT4a → Consider adjuvant cisplatin **or** ifosfamide-based chemotherapy (see Page 9)

No → Observation

cT2 → See Page 4

High risk T1[3] → 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] Cystoscopy combined with either cytology or fluorescence in situ hybridization (FISH) cytology as indicated. In selected patients, fluorescent cystoscopy should be considered.

[3] 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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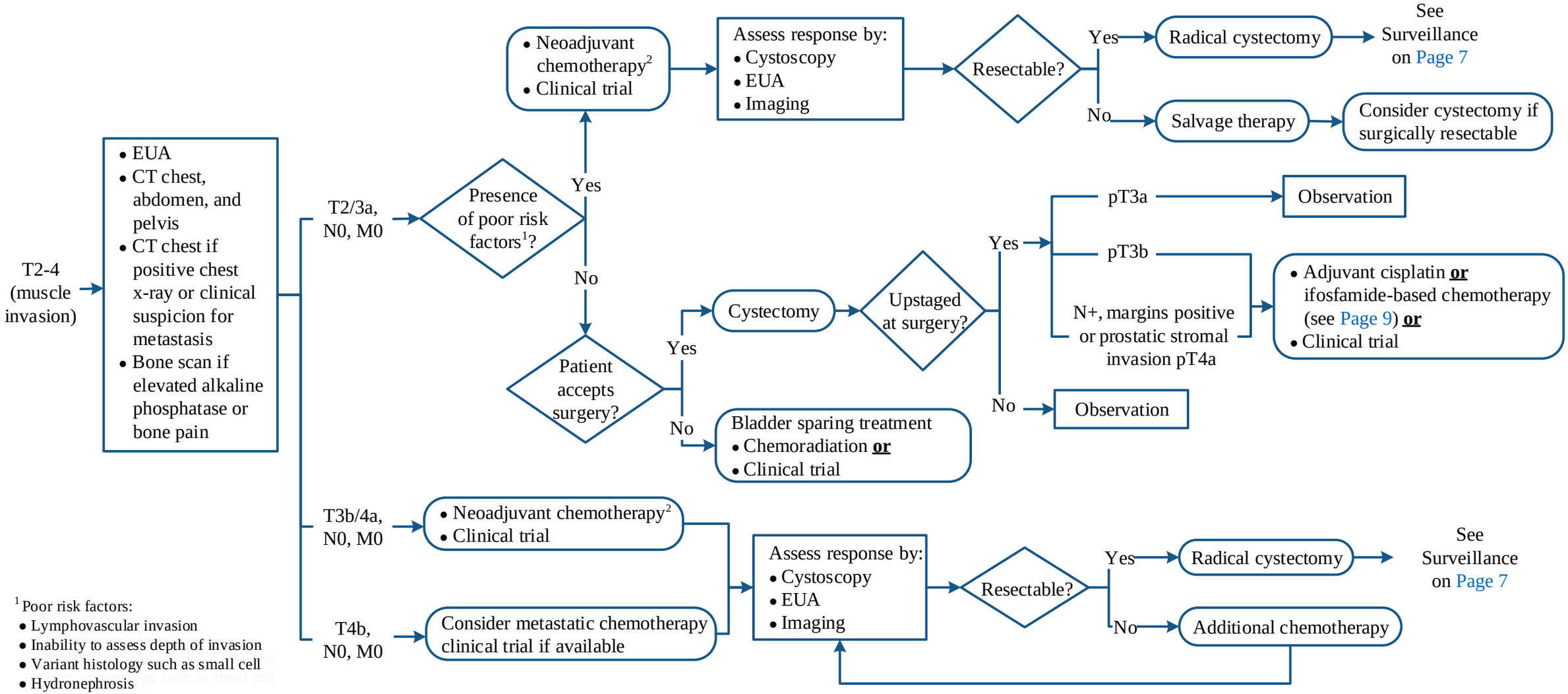
Urothelial Carcinoma of Bladder and Upper Tract

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

STAGE

TREATMENT AND FOLLOW-UP



[1] Poor risk factors:
- Lymphovascular invasion
- Inability to assess depth of invasion
- Variant histology such as small cell
- Hydronephrosis
- Tumor involving bladder diverticulum

[2] Consider neoadjuvant/adjuvant cisplatin or ifosfamide-based systemic chemotherapy (*i.e.*, DDMVAC, IAG, etc.). Refer to Principles of Systemic Therapy on Page 8

Urothelial Carcinoma of Bladder and Upper Tract

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

CLINICAL PRESENTATION

METASTATIC DISEASE

Any T, N+, M+[1]

- Positive pelvic nodes or
- Nodes below aortic bifurcation

→ Chemotherapy
- Consider metastatic clinical trial if available

→ CT chest, abdomen, and pelvis
- Bone scan

→ Assess response by:
- Cystoscopy
- EUA
- Imaging

→ Resectable[2]?

Yes → Surgical consolidation trials → See Surveillance on Page 7

No

Non-nodal metastasis

- Nodes above aortic bifurcation or
- Visceral metastasis

→ CT chest, abdomen, and pelvis
- Bone scan

A

Clinical trial or systemic treatment[3] as per patient's co-morbid medical conditions:

Front-line systemic treatment or clinical-trials:
- Cisplatin eligible:
  - GFR ≥ 50 mL/minute: full dose cisplatin or ifosfamide-based combinations (*i.e.*, DDMVAC, GC, IAG, ITP, GTP)
  - GFR ≥ 40 mL/minute and < 50 mL/minute: modified cisplatin-combinations including DDMVAC with split-dose cisplatin, GC with split-dose, CGI, or TMP
- Cisplatin ineligible:
  - Nephron-sparing combinations: GTA, GCtx, GVinorelbine
  - Pembrolizumab or atezolizumab may be consider for *PD-L1* high tumors

Second-line systemic treatment or clinical trials:
- *FGFR3* mutation or fusion:
  - Erdafitinib
- Wild type *FGFR3*:
  - Immune checkpoint inhibition: pembrolizumab, nivolumab, atezolizumab, durvalumab, 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 or clinical trials:
- Enfortumab vedotin (nectin-4 testing is not required)
- Ineligible for third-line treatment: consider alternative chemotherapy regimen from the front-line list of therapies or single agent taxane

DDMVAC = dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin
GC = gemcitabine and cisplatin
IAG = 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

[1] Consider mutation 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.
[3] See Appendix A for standard systemic treatments

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Urothelial Carcinoma of Bladder and Upper Tract

Disclaimer: *This algorithm has been developed for MD Anderson using a multidisciplinary approach considering circumstances particular to MD Anderson's specific patient population, services and structure, and clinical information. This is not intended to replace the independent medical or professional judgment of physicians or other health care providers in the context of individual clinical circumstances to determine a patient's care. This algorithm should not be used to treat pregnant women.*

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

CLINICAL PRESENTATION

Upper tract (renal pelvis or ureter) tumor

- CT urogram
- Cystoscopy
- Ureteroscopy
- Biopsy (forcep or brush) strongly recommended
- Washing adequate only if positive for high grade
- *MSI* testing

TREATMENT AND FOLLOW-UP

Low risk[1]

Patient suitable for conservative management[2]?

- Yes → Consider instillation of mitomycin gel (Jelmyto™) **or**; Holmium 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[3]?

- Yes → Consider adjuvant chemotherapy[4] **or** clinical trials
- No → Observation

High risk: High grade disease, sessile architecture, cT3 on imaging, or based upon clinical nomograms[1]

Consider:

- Multidisciplinary discussion for neoadjuvant **or** adjuvant chemotherapy[4]
- Clinical trial

→ Surgical removal (as above)

Metastatic disease

→ See Box A on Page 5

MSI = microsatellite instability

[1] See Appendix B and Appendix C for clinical risk nomograms
[2] 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)
[3] See Appendix D for postoperative nomogram for prediction of relapse-free survival
[4] Consider neoadjuvant/adjuvant cisplatin or ifosfamide-based systemic chemotherapy (*i.e.*, DDMVAC, IAG, etc.). Refer to Principles of Systemic Therapy on Page 9.

Urothelial Carcinoma of Bladder and Upper Tract

SURVEILLANCE AFTER RADICAL CYSTECTOMY

	Months								
	3	**6**	**12**	**18**	**24**	**30**	**36**	**48**	**60**[1]
Less than or equal to pT1 (no variant histology)[2]									
History[3] / PE / Laboratory[4]	x	x	x		x		x	x	x
Chest X-ray			x		x		x	x	x
CT urogram	x	x		x		x	x	x	
CT abdomen and pelvis		x[5]							
pT2 NO:									
History[3] / PE / Laboratory[4]	x	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	x
CT abdomen and pelvis		x		x					
pT3/T4 or pTxN+:									
History[3] / PE / Laboratory[4]	x	x	x	x	x	x	x	x	x
Chest X-ray	x	x	x	x	x	x	x	x	x
CT urogram			x		x		x	x	x
CT abdomen and pelvis	x	x		x		x			

PE = physical examination

[1] After 5 years, follow guidelines every 1-2 years at the discretion of the treating physician

[2] 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

[3] History should include urethral discharge/bloody mucus

[4] Laboratory tests include CBC, electrolytes, BUN, creatinine, and LFTs. Cytology is optional if imaging is routinely obtained.

[5] 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.

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 (TUR) of the tumor 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

PRINCIPLES OF SYSTEMIC THERAPY

Active agents:

- Two-to-three drug combinations based on cisplatin, docetaxel, paclitaxel, ifosfamide, gemcitabine or MVAC (methotrexate, vinblastine, doxorubicin, cisplatin) are used for treatment of metastatic disease. Adjuvant or neoadjuvant therapy is also considered for patients at high risk of recurrence.
- 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 LDH
  - Poor renal function
- Immunotherapy (pembrolizumab, nivolumab, atezolizumab, durvalumab, or avelumab) has been approved for patients failing frontline chemotherapy. *PD-L1* testing is not required.
- Atezolizumab and pembrolizumab are indicated front-line for cisplatin ineligible patients whose tumors are *PD-L1* high.
- 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.

PRINCIPLES OF SURGICAL MANAGEMENT

TRANSURETHRAL RESECTION OF BLADDER TUMOR (TURBT)

- The first step in surgical management of bladder tumors is a complete TUR of the tumor. Muscle must be present in the TUR 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 TUR 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 intravescical chemotherapy is most effective when given right after TUR (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)

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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 D5 1/4 NS IV plus mannitol 40 g/L with appropriate potassium and magnesium, 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 on Day 1 and Day 8 **and**
  Cisplatin 70 mg/m^2 IV on Day 1
  - Cisplatin followed with D5-1/4 NS IV plus mannitol 40 g/L with appropriate potassium and magnesium, typically for 3 liters

  This regimen is repeated every 3 weeks with growth factor support as needed

- Gemcitabine, Paclitaxel, Doxorubicin (GTA):
  Doxorubicin 30 mg/m2 IV **and**
  Paclitaxel 135 mg/m2 IV **and**
  Gemcitabine 900 mg/m2 IV

  This regimen is repeated every 2 weeks with growth factor support

- Ifosfamide, Doxorubicin, Gemcitabine (IAG):
  Ifosfamide 1500 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 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 on day 1 **and**
  Ifosfamide 1000 mg/m^2 IV on day 1 **and**
  Cisplatin 50 mg/m^2 IV on day 1
  - Cisplatin followed with 1/4 NS IV plus mannitol 40 g/L, typically for 3 liters

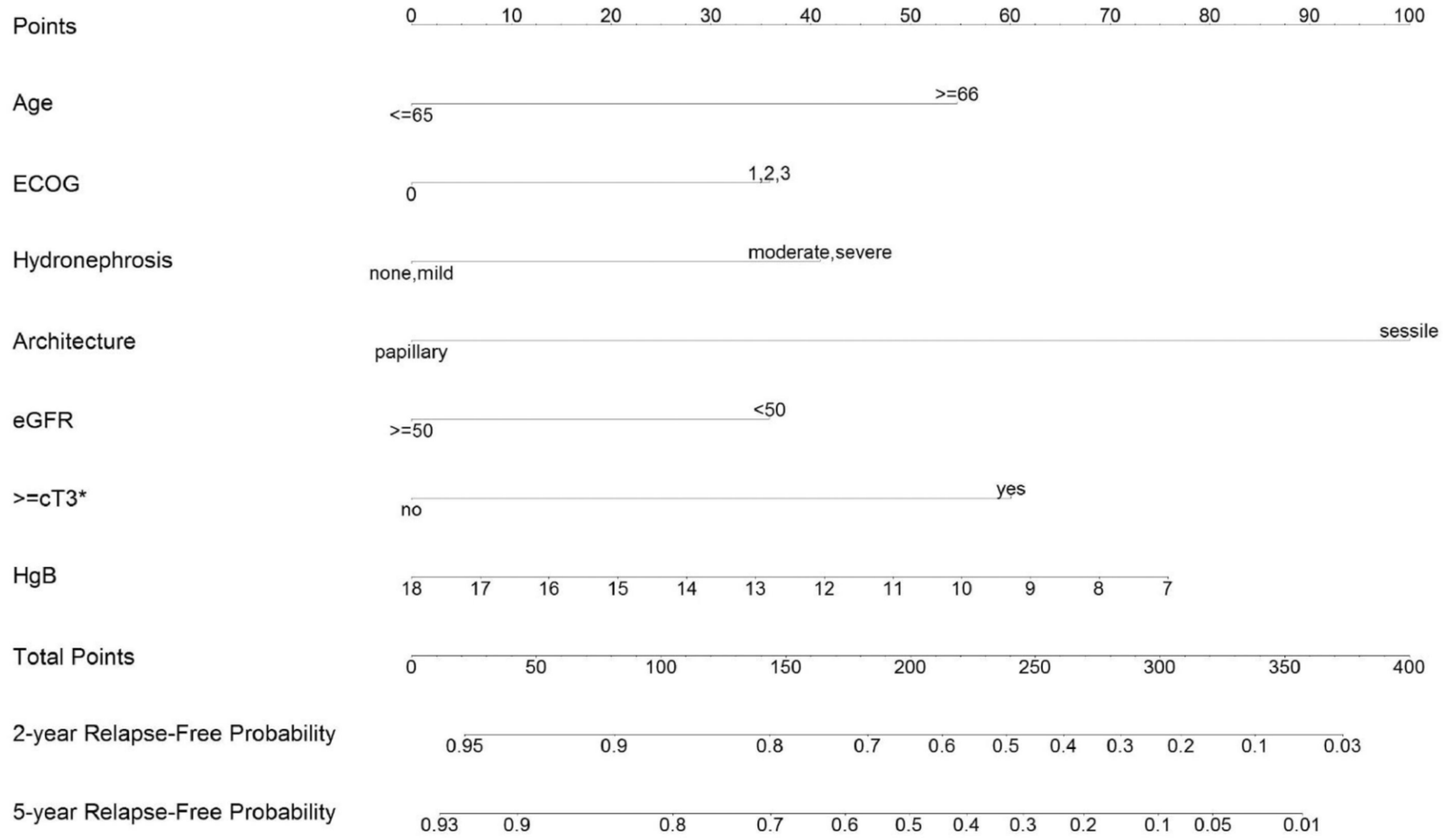
  This regimen is repeated every 2 weeks with growth factor support

Biotherapy and Targeted Therapy Regimens:

- Atezolizumab 1,200 mg IV every 3 weeks
- Avelumab 800 mg IV every 2 weeks
- Durvalumab 10 mg/kg IV every 2 weeks
- Enfortumab 1.25 mg/kg IV on days 1, 8, and 15 of every 4 weeks
- Erdafitinib 8 mg PO daily
  - May titrate up to 9 mg PO daily if phosphorous level on Day 15 is ≤ 5.5 mg/dL
- Nivolumab 240 mg IV every 2 weeks or 480 mg IV every 4 weeks
- Pembrolizumab 200 mg IV every 3 weeks or 400 mg IV every 6 weeks

APPENDIX B: Clinical Risk Nomograms

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

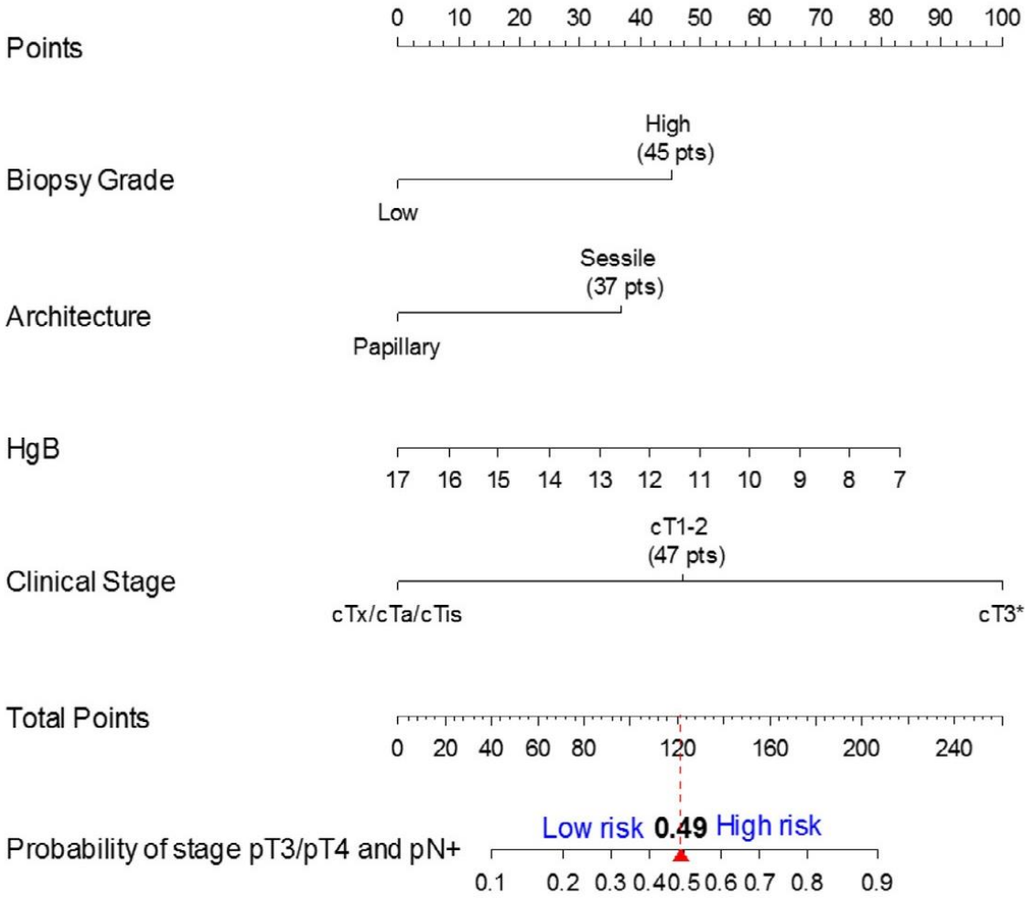


* based on imaging studies

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

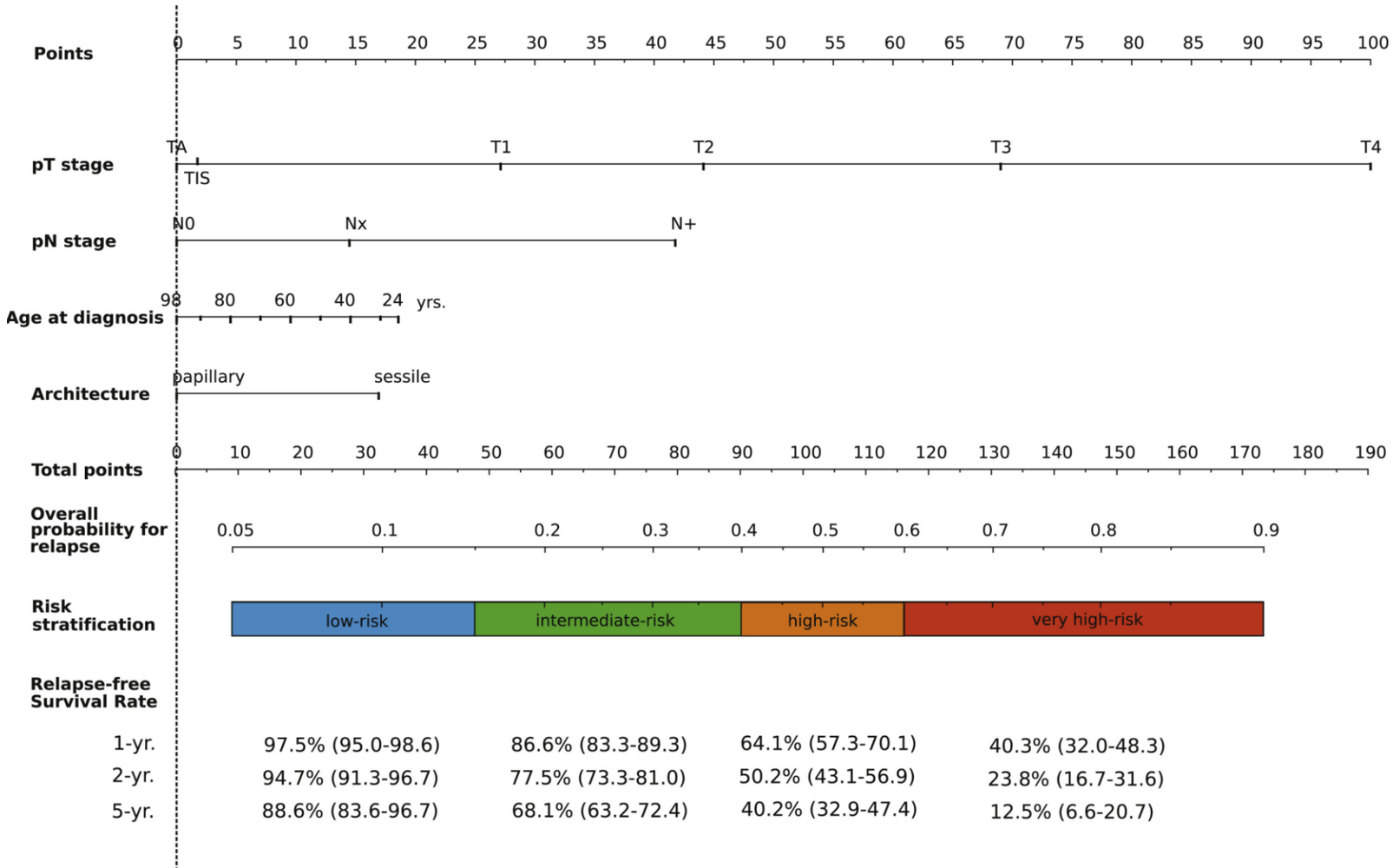
Preoperative probability of non-organ confined (pT3-4, N+) upper tract urothelial carcinoma, low or high grade



* 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*, p. 292.e6. Copyright 2018 by Elsevier Inc. Reprinted with permission.

APPENDIX D: Postoperative nomogram for prediction of relapse-free survival



Relapse-free Survival Rate

1-yr.	97.5% (95.0-98.6)	86.6% (83.3-89.3)	64.1% (57.3-70.1)	40.3% (32.0-48.3)
2-yr.	94.7% (91.3-96.7)	77.5% (73.3-81.0)	50.2% (43.1-56.9)	23.8% (16.7-31.6)
5-yr.	88.6% (83.6-96.7)	68.1% (63.2-72.4)	40.2% (32.9-47.4)	12.5% (6.6-20.7)

From "Postoperative nomogram for relapse-free survival in patients with high grade upper tract urothelial carcinoma," by L.-M. Krabbe, O. Eminaga, S. F. Shariat, R. C. Hutchinson, Y. Lotan, A. I. Sagalowsky, . . . V. Margulis, 2017, *The Journal of Urology*, *197*, p. 583. Copyright 2017 by American Urological Association Education and Research, Inc.. Reprinted with permission.

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Continued on next page

SUGGESTED READINGS – continued

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