Protocols of Muscle-invasive and Metastatic Bladder Cancer

با همکاری

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قطب ارولوژی کشور

Table 1. Bladder cancer staging and classification†

	Stage and Stage grouping		Stage description
Non- muscle invasive Bladder cancer (NMIBC) [AP1]	Stage 0a : TaN0M0		The cancer is a noninvasive papillary carcinoma (Ta). It has grown toward the hollow center of the bladder but has not grown into the connective tissue or muscle of the bladder wall.
	Stage 0is: TisN0M0		The cancer is a flat, noninvasive carcinoma (Tis), also known as flat carcinoma in situ (CIS). The cancer is growing in the inner lining layer of the bladder only. It has not grown inward toward the hollow part of the bladder, nor has it invaded the connective tissue or muscle of the bladder wall.
	Stage I: T1N0M0		The cancer has grown into the layer of connective tissue under the lining layer of the bladder but has not reached the layer of muscle in the bladder wall (T1).
Muscle invasive Bladder cancer (MIBC)	Stage II [AP2] : (T2a or T2b) ; N0 ; M0		The cancer has grown into the inner (T2a) or outer (T2b) muscle layer of the bladder wall, but it has not passed completely through the muscle to reach the layer of fatty tissue that surrounds the bladder.
	Stage IIIA[AP3,4]	(T3a, T3b or T4a) ; N0; M0	The cancer has grown through the muscle layer of the bladder and into the layer of fatty tissue that surrounds the bladder (T3a or T3b). OR It may have spread into the prostate, uterus, or vagina, but it is not growing into the pelvic or abdominal wall (T4a).
		(T1-4a); N1; M0	The Cancer has grown into the layer of connective tissue under the lining of the bladder wall (T1), OR into the muscle layer of the bladder wall (T2), OR into the layer of fatty tissue that surrounds the bladder, (T3a or T3b) OR It may have spread into the prostate, uterus, or vagina, but it is not growing into the pelvic or abdominal wall (T4a). AND the cancer has spread to a nearby lymph node in the true pelvis (N1).
	Stage IIIB	(T1-T4a); N2 or N3; M0	The cancer has grown into the layer of connective tissue under the lining of the bladder wall (T1), OR into the muscle layer of the bladder wall (T2), OR into the layer of fatty tissue that surrounds the bladder (T3a or T3b), OR it may have spread into the prostate, uterus, or vagina, but it is not growing into the pelvic or abdominal wall (T4a). AND the cancer has spread to 2 or more lymph nodes in the true pelvis (N2) or to lymph nodes along the common iliac arteries (N3).
	Stage IVA	T4bN0M0	The cancer has grown through the bladder wall into the pelvic or abdominal wall (T4b). BUT has not spread to nearby lymph nodes (N0) or to distant sites (M0)
		Any T; Any N; M1a	The cancer may or may not have grown through the wall of the bladder into nearby organs (Any T). It may or may not have spread to nearby lymph nodes (Any N). BUT It has spread to a distant set of lymph nodes (M1a).
	Stage IVB	Any T; Any N; M1b	The cancer may or may not have grown through the wall of the bladder into nearby organs (Any T). It may or may not have spread to nearby lymph nodes (Any N). It has spread to 1 or more distant organs (such as the bones, liver or lungs) (M1b).

†According to American Joint Committee on Cancer/International Union Cancer Consortium 2017 Tumor, Nodes, and Metastases (TNM) Staging Classification

Table 2. Treatment of various urothelial bladder cancers[1]

Variant name	Specifications and special considerations	Treatment
Micropapillary	–	Neoadjuvant chemotherapy + Early cystectomy and lymphadenectomy with any amount of this variant (even if T1)
Sarcomatoid (Carcinosarcoma)	• Poor response to chemotherapy • Worse outcome than pure urothelial cancer	Immediate cystectomy
Plasmacytoid	• Aggressive phenotype • Chemosensitive	Neo-adjuvant chemotherapy + Radical cystectomy
Nested	• Aggressive but having similar prognosis to pure urothelial carcinoma	Radical cystectomy + chemotherapy

Table 3. Treatment of non-urothelial bladder cancers[1-3]

Cancer type	Specifications and special considerations	Treatment
Small cell carcinoma	• highly aggressive • no need for preventive brain irradiation to avoid brain recurrence	Neo adjuvant chemotherapy + Radial cystectomy or Bladder preservation protocol
Squamous cell carcinoma	• usually advanced at the time of diagnosis	Primary radical cystectomy and .lymphadenectom
Primary (glandular) Adenocarcinoma*	• No chemotherapy or radiation	Radical cystectomy and lymphadenectomy
Urachal remnant Adenocarcinoma[a]	• Located in the dome or urachal ligament or umbilicus	En-bloc resection of bladder dome + urachal ligament + umbilicus

[a] Two other types of bladder adenocarcinoma are: 1) Secondary: due to invasion from colon or prostate or endometrium and 2) Metastatic

Primary evaluation of MIBC patients[1, 3, 4][AP5]

1. Transurethral resection of bladder tumor (TURBT) [AP6]
2. Bimanual examination under general anesthesia (EAU)[AP7]
3. Complete blood count (CBC) and Chemistry profile, including alkaline phosphatase
4. Liver function test (LFT)
5. Chest imaging
    a. Chest CT-scan (preferred modality)

    OR

    b. Chest X-ray (PA, Lateral)
6. Abdominopelvic imaging
    a. CT- scan (+ Contrast) [AP8]

    OR

    b. MRI In case of any contraindications for CT-Scan [AP9]

    OR

    c. Ultrasound + Retrograde pyelography if both CT and MRI are contraindicated

7. U/A, U/C, Serum creatinine, and Estimated GFR
8. Bone Scan; if Clinically suspected, symptoms of bone metastasis or raised serum ALP
9. Brain imaging; in symptomatic patients or high risk subtypes (e.g., small cell carcinoma)
10. Prostatic biopsy (as indicated) [AP10,11]
11. FDG PET-CT scan (as indicated) [AP12]

Prognostic predictors after radical cystectomy[1]

- Pathologic stage
- Lymph node extension

- Positive Margin

Principles of chemotherapy[4]

- Described in detail at the end of Appendix (Page 17)

Principles of urethral tumoral involvement and recurrence[1]

- Indicators of prostatic urethral involvement are involvement of the bladder neck, multiple bladder tumors, positive cytology and CIS
- Predictors for distal urethral involvement in females are tumor at bladder neck (40%), vaginal involvement and inguinal lymphadenopathy
- Indications of distal urethrectomy include diffuse prostatic urethral or ductal involvement with CIS, non-muscle invasive bladder cancer and positive apical margin (the most reliable predictor for distal urethrectomy)
- Risk factors of urethral recurrence include: prostatic stroma involvement (up to 80% more chance than prostatic urethral involvement) and non- muscle invasive bladder cancer
- A 4-8% risk of recurrence in urethral remnant has been reported after cystoprostatectomy (mostly symptomatic).

Principles of ureteral tumoral involvement and recurrence[1]

- Risk factors for upper tract recurrence are : bladder CIS, distal ureteral involvement and high grade Ta-T1
- Risk of upper tract recurrence was higher in those with a positive margin on first frozen section even if the distal ureter was further resected in order to obtain a negative final margin.
- Ureteral skip lesion has been reported in 4.8% cases (positive proximal margin in permanent pathology with negative distal frozen section).

- In case of distal ureteral CIS, resect as high as possible, without jeopardizing the ureteral length required for the subsequent diversion procedure.
- Prevalence of ureteral involvement at the time of cystectomy is 6 - 8%
- Recurrence of urothelial carcinoma in the upper tract after radical cystectomy is 2 - 8%.

Table 4. TREATMENT AND FOLLOW-UP OF STAGE II (T2a or T2b)N0M0[3, 4]

<table>
<tr><th>Primary treatment</th><th colspan="3">Following cystectomy / bladder sparing protocol</th><th>Follow up</th></tr>
<tr><td>Neoadjuvant + Radical cystectomy AP13-20+ classic/extended lymphadenectomy AP21-29

Or

NeoadjuvantAP30-35+ Partial CystectomyAP38-40

Or

Cystectomy alone (for those not eligible for cisplatin)</td><td colspan="3">Based on pathologic risk,
1. If no cisplatin neoadjuvant treatment given and T3 or T4a or pN+
Either
❖ Adjuvant[AP36,37] cisplatin-based chemotherapy (preferred)
Or
❖ adjuvant nivolumab

Or

2. If cisplatin neoadjuvant chemotherapy given and T2-T4a or N+, consider nivolumab

Or

3. Adjuvant RT (T3–4, N+ & margin +)</td><td>Table 5</td></tr>
<tr><td rowspan="2">Bladder preservation with concurrent chemoradiotherapyAP41-43</td><td rowspan="2">Reassess tumor status 2-3 Months after treatment completion</td><td>tumor</td><td>If Tis, Ta or T1→ intravesical BCG
Or
Surgical consolidation
Or
Treat as metastatic disease</td><td rowspan="3">Table 6</td></tr>
<tr><td>No tumor</td><td>Surveillance and follow up</td></tr>
<tr><td>If patient prefers bladder preservationAP44 :

Concurrent chemoradiotherapy

Or</td><td>Reassess tumor status 2-3</td><td>Tumor</td><td>Chemoradiotherapy
Or
Radiotherapy
Or
TURBT + BCG</td></tr>
</table>

RT **Or** **TURBT[AP45,46] (Complete or visually complete or maximally TURBT)**	Months later	No tumor	Surveillance and follow up	

Table 5. Post-Cystectomy Muscle Invasive Bladder Cancer Follow-up[3, 4]

test	**year**						
	1	**2**	**3**	**4**	**5**	**5-10**	**>10**
cystoscopy	N/A (due to prior cystectomy)						
imaging	•CTU or MRU (image upper tracts + axial imaging of abdomen/pelvis) every 3-6 months •CT chest (preferred) or chest x-ray every 3-6 months or •FDG PET/CT only if metastatic disease suspected		• Abdominal/pelvic CT or MRI annually • CT chest (preferred) or chest x-ray annually or • FDG PET/CT only if metastatic disease suspected			abdominopelvic US annually	
Blood test	•Renal function testing (electrolytes and creatinine) every 3-6 months •LFT every 3-6 months •CBC, CMP[AP46] every 3-6 months if received chemotherapy •acid-base evaluation in case of intestinal utilization every 6 months		• Renal function testing (electrolytes and creatinine) annually • LFT annually • Vitamin B12 annually			•CBC, Renal Function testing (electrolytes and creatinine), B12 annually •Any other tests if indicated	
Urine test	•Urine cytology every 6 months		•Urine cytology as clinically indicated •Urethral wash cytology as clinically indicated				

	•Consider urethral wash cytology every 6 months	

Table 6: Post-Bladder Sparing (ie, Partial Cystectomy or Chemoradiation) Follow-up [3, 4]

test	**year**						
	1	**2**	**3**	**4**	**5**	**5-10**	**>10**
cystoscopy	Every 3 month		Every 6 month		annually		As clinically indicated
imaging	•CTU or MRU (image upper tracts + axial imaging of abdomen/pelvis) every 3-6 months •CT chest (preferred) or chest x-ray every 3-6 months or •FDG PET/CT only if metastatic disease suspected		• Abdominal/pelvic CT or MRI annually • CT chest (preferred) or chest x-ray annually or • FDG PET/CT only if metastatic disease suspected			As clinically indicated	
Blood test	•Renal function testing (electrolytes and creatinine) every 3-6 months •LFT every 3-6 months •CBC, CMP every 3-6 months if received chemotherapy		• Renal function testing (electrolytes and creatinine) As clinically indicated • LFT As clinically indicated				

Table 7. TREATMENT AND FOLLOW-UP OF STAGE IIIa (T3a, T3b or T4a)N0M0 OR (T1-4a)N1M0[3, 4]

<table>
<tr><th>Primary treatment</th><th colspan="3">Following cystectomy / bladder sparing protocol</th><th>Follow up</th></tr>
<tr><td>Neoadjuvant cisplatin-based combination chemotherapy followed by radical cystectomy

Or

Cystectomy alone for those not eligible to receive cisplatin-based chemotherapy</td><td colspan="3">Based on pathologic risk,
1. If no cisplatin neoadjuvant treatment given and pT3, pT4a, or pN+
Either
❖ Adjuvant cisplatin-based chemotherapy should be discussed (preferred)
Or
❖ Consider adjuvant nivolumab

Or

2. If cisplatin neoadjuvant chemotherapy given and ypT2-ypT4a or ypN+, consider nivolumab

Or

3. Consider adjuvant RT in selected patients (T3–4, positive nodes/margins)[AP47]</td><td>Table 5</td></tr>
<tr><td rowspan="2">Bladder preservation with concurrent chemoradiotherapy</td><td rowspan="2">Reassess tumor status 2-3 Months after treatment completion</td><td>tumor</td><td>If Tis, Ta or T1, consider intravesical BCG

Or

Surgical consolidation

Or

Treat as metastatic disease</td><td rowspan="2">Table 6</td></tr>
<tr><td>No tumor</td><td>surveillance</td></tr>
</table>

If patient prefers bladder preservation or is unable to undergo cystectomy: Concurrent chemoradiotherapy **Or** **RT**	Reassess tumor status 2-3 Months after treatment completion	Tumor	Systemic therapy **Or** TURBT ± intravesical therapy **And** Best supportive care	
		No tumor	surveillance	

Lymph node dissection principles

Bilateral pelvic lymphadenectomy should be performed including internal iliac, external iliac, and obturator lymph nodes. Additionally, In case of gross lymphadenopathy in the classic site, common iliac lymphadenectomy is recommended [2-4].

Table 8. TREATMENT AND FOLLOW-UP OF STAGE IIIb (T1-T4a)(N2-N3)M0[3, 4]

Primary treatment	**Following cystectomy / bladder sparing protocol**			**Follow up**
Downstaging systemic therapy	Reassess tumor status 2-3 months after treatment Unless there is indication for early intervention	Complete response	Consolidation cystectomy + Extended lymphadenectomy if possible **Or** Consolidation chemoradiotherapy **Or** Surveillance	In case of cystectomy : Table 5 in case of bladder preservation : Table 6
		Partial response	Cystectomy **Or** Chemoradiotherapy **Or** Treat as metastatic disease	In case of cystectomy : Table 5 in case of bladder preservation : Table 6 in case of metastasis : Table 11
		Progression	Treat as metastatic disease	Table 11
		Complete response	Follow up	Table 6

Concurrent chemoradiotherapy	Reassess tumor status 2-3 months after treatment Unless there is indication for early intervention	Partial response	If Tis, Ta or T1, consider intravesical BCG **Or** Surgical consolidation **Or** Treat as metastatic disease	In case of cystectomy : Table 5 in case of bladder preservation : Table 6 in case of metastasis : Table 11
		Progression	Treat as metastatic disease	Table 11

Table 9. TREATMENT AND FOLLOW-UP OF STAGE IVa (T4bN0M0) OR (Any T, Any N, M1a)[3, 4]

	Primary treatment	**Following cystectomy / bladder sparing protocol**			**Follow up**
M0 disease	Systemic therapy	After 2-3 cycles, reassess with cystoscopy, EUA, TURBT, and imaging of abdomen/pelvis	No Tumor	Consider consolidation systemic therapy Or Chemoradiotherapy (if no previous RT) And/Or Cystectomy	In case of cystectomy : Table 5
			Tumor present	Systemic therapy Or Chemoradiotherapy (if no previous RT) And/Or Cystectomy	

	Concurrent chemoradiotherapy	Reassess tumor status 2-3 months after treatment	No Tumor	Consider consolidation systemic therapy Or Chemoradiotherapy (if no previous RT) And/Or Cystectomy	in case of bladder preservation : Table 6 in case of metastasis : Table 11
			Tumor present	Systemic therapy Or Chemoradiotherapy (if no previous RT) And/Or Cystectomy	
M1a disease	Systemic therapy	Evaluate with cystoscopy, EUA, TURBT, and imaging of abdomen/pelvis	Complete response	Consider consolidative local therapy in selected cases	
			Stable disease or progression	Treat as metastatic disease	

Table 10. TREATMENT AND FOLLOW-UP OF Metastatic DISEASE [3, 4]

Additional workup	Primary treatment	Follow up
• Bone scan if clinical suspicion or symptoms of bone metastases • Chest CT • Consider central nervous system (CNS) imaging • Estimate GFR to assess eligibility for cisplatin • Consider biopsy if technically feasible •Molecular/genomic testing	Systemic therapy and/or Palliative RT and/or palliative cystectomy	Table 11

[#]According to National Comprehensive Cancer Network (NCCN) and European Association of Urology (EAU) MIBC protocols.

Table 11: Metastatic disease Follow-up [3, 4]

test	year						
	1	2	3	4	5	5-10	>10
cystoscopy	• Every 3–6 mo as clinically indicated						
imaging	•CTU or MRU (image upper tracts + axial imaging of abdomen/pelvis) every 3-6 months if clinically indicated and with any clinical change or new symptoms •CT chest/abdomen/pelvic every 3–6 months and with any clinical change or new symptoms Or •FDG PET/CT						
Blood test	•CBC, CMP every 1–3 months •B12 annually for patients who had undergone a cystectomy						
Urine tests	•Urine cytology as clinically indicated						

Appendix

1. NMIBC is further subdivided into low-, intermediate-, and high-risk disease. Low-risk NMIBC comprises a primary (i.e., not recurrent), low-grade papillary (Ta), solitary tumors less than 3 cm[5]. Intermediate-risk NMIBC is histologically confirmed by multiple and/or recurrent and/or large (>3 cm) low-grade Ta tumors. High-risk NMIBC involves tumors with any high-grade histologic features (i.e., CIS or T1). In addition, the 2017 AJCC recommends subcategorization of T1 urothelial carcinoma into T1a (superficial) and T1b (deep) lamina propria invasion to help stratify the heterogeneous group of T1 tumors, which are at a 50% risk of upstaging to T2 or higher and a 33% risk of being upstaged to non–organ confined. These stratifications suggest that the deeper the tumor invades into the lamina propria, the worse the survival [6].
2. Degree of muscular invasion cannot be reliably differentiated with TURBT[7].
3. Invasion to prostatic urethra has no adverse prognosis[1, 8].
4. Nodal involvement without evidence of systemic disease is classified as stage 3[4].
5. There is a possible discrepancy between clinical and subsequent pathological staging[6].

Clinical Staging	Pathological staging
CT2	PT3(40%)
CT2	PT4(9%)
CT2	N+(25%)

6. Advantages of TURBT include: reduction of tumor burden, optimizing response to Neo-Adjuvant chemotherapy, increasing the chance for bladder preservation with trimodal therapy, and better survival at radical cystectomy irrespective of adjuvant chemotherapy (in stages T0- T3)[1, 9].
7. Findings of Bimanual exam in emptied bladder: (T2a : No palpable mass), (T2b: induration but no three-dimensional mass), (T3a : mobile three – dimensional mass), (T4a : a mass which has invaded adjacent organs), (T4b : mass which is fixed to pelvic sidewalls)[1, 10].
8. CT-scan must be obtained either before TURBT or 7 days post TURBT. CT-scan helps in staging, detecting possible lymphadenopathy, and hydronephrosis[1, 11].
9. MRI (± contrast) can be more accurate than CT-scan for staging, predicting tumor grade, and chemosensitivity; but is not trustable for lymph node detection[1, 11].
10. Indications are : carcinoma in-situ in bladder, tumor in bladder neck, positive cytology without evidence of tumor in the bladder, and abnormal prostatic urethra[1, 12].
11. Deep prostatic biopsy must be taken from mid-prostate to mid or distal verumontanum (5 and 7 O'clock adjacent to verumontanum). This can replace apical intraoperative frozen section. In female patients, bladder neck biopsy is sufficient for orthotopic bladder decision[1, 3].
12. May have a limited role in special clinical scenarios or in patients with a previously suspicious imaging. May improve lymph node detection [1, 11].
13. Radical cystectomy is the gold-standard treatment for MIBC [1-4, 13].
14. Cystectomy is not recommended in case of: impossibility of lymphadenectomy, extensive peri-ureteral invasion, bladder fixation to side walls or invasion to rectosigmoid[1].
15. 80% of MIBC patients who have received definitive management have had radical cystectomy [1].
16. Only 4% local recurrence reported after radical cystectomy with negative lymph node [1].

17. In case of a tumor located in bladder dome, adjacent attached peritoneum can be resected with the tumor.
18. Prostate capsule sparing radical cystectomy can be considered in potent patients, without any evidence of tumor in bladder neck, have a negative deep prostatic urethral biopsy and normal serum PSA. Nerve sparing radical cystectomy can be considered in potent patients with clinical applicability of the procedure [2-4].
19. Conclusively, according to our consensus, sexual-preserving techniques (nerve-sparing, prostate capsular-sparing …) should be offered to men motivated to preserve their sexual function since the majority will benefit. Select patients based on: • organ-confined disease; • absence of any kind of tumor at the level of the prostatic stroma.

    However it's noteworthy that according to EAU and AUA guidelines sexual-preserving procedures must be reserved for patients whose bladder neck, urethra, and prostate are intact [2-4].
20. Sexual organ-preserving techniques should be offered to women motivated to preserve their sexual function since the majority will benefit. Select patients based on: • absence of tumor in the area to be preserved to avoid positive soft tissue margins; • absence of pT4 urothelial carcinoma [2-4].
21. Pelvic lymphadenectomy (P.L) can improve outcome and local control and has an acceptable morbidity [1, 3, 4, 14].
22. 25% of patients have positive lymph nodes [1].
23. P.L definitions [1, 3, 4, 14] :
    a. Standard P. L= obturator + internal iliac + external iliac
    b. Extended P.L = standard+ common iliac, not more than 2cm of inferior aorta
    c. Super extended P.L. = Up to inferior mesenteric artery
24. Primary landing zone of lymph nodes include: internal and external iliac, obturator, and presacral[1].
25. Adequate lymph node dissection and exact therapeutic control are less clear[1].
26. In case of adenopathy at surgery an extended lymphadenectomy is suggested[1, 3, 4].
27. The exact number of lymph node removal for survival benefit is not clear, but most studies have reported a threshold of 15-19 nodes. Probability of positive node based on total number of nodes

removed is as following: (50 nodes = 90%), (25 nodes = 70%; reasonable cutoff), (15-25 nodes = 50%)[1].

28. Lymph node density is an area of controversy, but most of the scholars accept < 20% as an indicator for better 5-year disease-specific survival (DSS) and response to adjuvant chemotherapy. Additionally, Extra nodal extension is also an independent prognostic for OS/DSS[1].
29. P.L is the most powerful surrogate for long-term overall survival (OS) and relapse-free survival (RFS)[1].

30. Advantages of neoadjuvant chemotherapy[1-4, 15-17].
    a. Chemotherapy is better tolerated before surgery.
    b. If present, micro metastasis better responds to chemotherapy when smaller.
    c. Can potentially downstage bully or locally advanced tumor thus resulting in higher rates of margin negative tumors.
31. Disadvantage of neoadjuvant chemotherapy [1-4, 15-17]
    a. Delayed treatment (cystectomy) in case of chemo-resistant tumors.
32. 5-year OS of Neoadjuvant + cystectomy patients is 54% while it is 43% in patients who have undergone only cystectomy [1].
33. In PT0 patients 80% alive at 5-year vs 40% in patients with residual disease [1].
34. No significant benefit of neoadjuvant considering 5-year OS (5%); however there isn't any well-designed prospective study in this regard[1].
35. Based on meta-analysis there is a 5%-6% OS benefit for neoadjuvant and 30%-40% PT0 at cystectomy[1].
36. All T3a, T3b, and T4a or node positive patients who have not undergone neoadjuvant chemotherapy must be offered adjuvant chemotherapy [1-4].

37. Limitations of adjuvant chemotherapy include: Patient deconditioning, deterioration of renal function, perioperative complications, and a lack of clear evidence for the benefit of adjuvant chemotherapy because of inadequate prospective studies [1-4].
38. Indications of partial cystectomy include: Small solitary tumor, possible resection even with 2.5cm of normal urothelium (margin), away from ureteral orifice and suitable location, no CIS in the bladder, random biopsy is negative preoperatively, frozen section biopsies of margins are negative [1-4].
39. Considering the abovementioned criteria, long term outcomes are comparable to radical cystectomy with 12-50%, 17-57%, and 14-52% recurrence in non-muscle invasive, muscle invasive and metastatic patients, respectively[1, 18].
40. A relatively new modality of treatment consists of neoadjuvant radiation and chemotherapy followed by partial cystectomy and bilateral pelvic lymphadenectomy [19].
41. Indications of Trimodality bladder preservation includes: fit patient, tumor <4cm, unifocal, stage lower than T3, no hydronephrosis, grossly totally resectable, patient motivation for bladder preservation, no diffuse CIS, no long-life expectancy [1, 3, 20].
42. 25-30% cases who have previously underwent trimodality bladder preservation, will need to do salvage cystectomy ultimately [1, 21]
43. At 5-year follow up, 80% of patients who have undergone trimodality bladder preservation are still alive, but 57% had an intact bladder [1, 22].
44. Bladder preservation in Stage 2 should only be considered if no hydronephrosis and no CIS are seen, tumor is <6cm or patient is unable to undergo cystectomy [2-4].
45. Indications for TUR.BT Monotherapy include: Tumor <3cm, no hydronephrosis, no tumor on repeat cystoscopy, Unifocal tumor, no lymphadenopathy [2-4].
46. In case of TUR.BT Monotherapy intensive follow up is necessary [2-4].
47. A comprehensive metabolic panel(CMP) comprises 14 different determinants: glucose, calcium, sodium, potassium, carbon dioxide, chloride, albumin, total protein, alkaline phosphatase(ALP),

alanine transaminase (ALT), aspartate transaminase (AST), bilirubin, blood urea nitrogen (BUN) and creatinine (Cr)[23, 24].

48. According to EAU guidelines, adjuvant radiation should be considered in addition to chemotherapy following RC, based on pathologic risk (pT3b–4 or positive nodes or positive margins)[3].

Principles of Chemotherapy[4]

- First-line treatment for platinum-fit patients :
    a. Use cisplatin-containing combination chemotherapy with GC (gemcitabine and cisplatin)or HD-MVAC (high dose methotrexate, vinblastine sulfate, doxorubicin hydrochloride (Adriamycin), and cisplatin).
    b. In patients unfit for cisplatin but fit for carboplatin, use the combination of carboplatin and gemcitabine.
- First-line treatment in patients unfit for platinum-based chemotherapy
    a. Consider checkpoint inhibitors pembrolizumab or atezolizumab in case of high PD-1 expression.
- Second-line treatment
    a. Offer checkpoint inhibitor pembrolizumab to patients progressing during, or after, platinum based combination chemotherapy for metastatic disease.

Table 12: Definitions of platinum-eligibility for first-line treatment of metastatic urothelial carcinoma

Platinum-eligible		Platinum-ineligible
Cisplatin-eligible	Carboplatin-eligible	
ECOG PS 0-1 and	ECOG PS 2 or GFR 30–60 mL/min	Any of the following:
GFR > 50–60 mL/min and	or not fulfilling other cisplatin eligibility criteria	GFR < 30mL/min
Audiometric hearing loss grade < 2 and		ECOG PS > 2
Peripheral neuropathy grade < 2 and		ECOG PS 2 and GFR < 60 mL/min
Cardiac insufficiency NYHA class < III		Comorbidites > Grade 2

ECOG = Eastern Cooperative Oncology Group; GFR = glomerular filtration rate; NYHA = New York Heart Association; PS = performance status.

Table 13. Performance status scale according to Eastern Cooperative Oncology Group (ECOG)

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

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