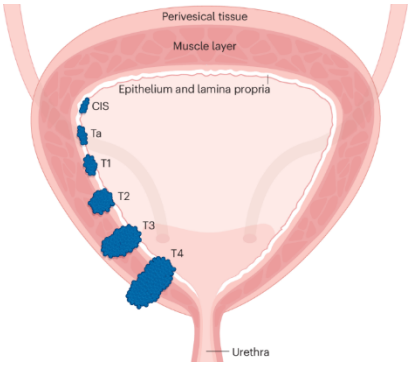
MUSCLE-INVASIVE BLADDER CANCER

General Overview

- 9th leading cause of cancer worldwide (13th leading cause of cancer deaths)
- Presentation: most frequently **painless hematuria**, irritative voiding symptoms
- Most frequent in men ≥60 years
- Risk factors: **smoking**, history of non-muscle invasive bladder cancer. To a lesser extent occupational exposure to carcinogens, chronic irritation, previous radiotherapy
- Histology: 90% **urothelial carcinoma (UCC)** (most common in Europe and USA), squamous cell carcinoma (due to long-term irritation or infection), adenocarcinoma, rarer or mixed histologies.

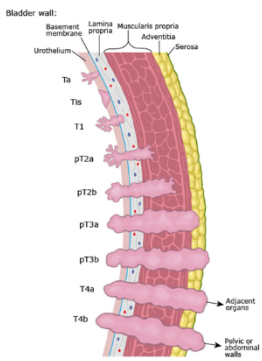


Diagnostic work up and staging

- Urine cytology (omit if imaging-based diagnosis is present)
  - negative cytology does not exclude bladder cancer
  - does not differentiate between non-muscle invasive and muscle invasive bladder cancer
- Flexible cystoscopy & biopsy (omit if imaging-based diagnosis is present)
- Transurethral resection of bladder tumor (TURB)
- Upper tract imaging with CT IVP (2.5% synchronous upper tract UCC); if indicated ureteroscopy
- If pT2-4 (= muscle-invasive): CT thorax-abdomen-pelvis

Primary Tumor (T)	Regional Lymph Nodes (N)	Distant Metastasis (M)
Tx: Primary tumor cannot be assessed **T0**: No evidence of primary tumor **Ta**: Noninvasive papillary carcinoma **Tis**: Carcinoma in situ: "Flat tumor" **T1**: Invasion lamina propria **T2**: Invasion muscularis propria **pT2a**: Superficial (inner half) **pT2b**: Deep (outer half) **T3**: Invasion perivesical soft tissue **pT3a**: Microscopically **pT3b**: Macroscopically **T4**: Tumor invades: **pT4a**: Prostatic stroma, seminal vesicles, uterus, vagina **pT4b**: Pelvic wall, abdominal wall	**Nx**: LN cannot be assessed **N0**: No regional LN **N1**: Single regional LN in true pelvis: perivesical, obturator, internal/ external iliac, sacral **N2**: Multiple regional LN in true pelvis **N3**: Common iliac LN	**M0**: No distant M+ **M1**: Distant M+ **M1a**: LN beyond common iliacs **M1b**: Non-LN distant M+

- Stage 0: noninvasive papillary carcinoma (Ta) and carcinoma in situ (Tis)
- Stage 1: non-muscle-invasive bladder cancer (T1N0)
- Stage 2: muscle-invasive bladder cancer (T2N0)
- Stage 3: locally advanced tumor and/or LN involvement
- Stage 4: T4b or metastatic disease



Treatment

Non-metastatic bladder cancer

- *Before platinum-based chemotherapy, obtain: biochemistry incl kidney function, audiometry, G8 geriatric screening (if ≥75 years old), in young pts discuss cryopreservation & fertility-preserving surgery.*
- *If cisplatinum-ineligible due to hydronephrosis: consider nephrostomy to allow kidney function to improve (without delaying planning of surgery)*

Operable MIBC (cT2-T4a N0-1)

Neo-adjuvant chemotherapy:

- In all pts who are cisplatinum eligible
  - Very fit pts: 6x dd-MVAC q2w
  - Others: 4x cisplatinum-gemcitabine q3w.
    - If well tolerated and cT4 or N+: 6x.
    - If poorly tolerated: consider continuing at split-dose, at the cost of inferior outcomes
- CT Tx-abdomen + consultation urology after last cycle
- Provisional surgery date to be planned during MTB at start of neo-adj Tx. In case of delay or early stop, alert onconurse

Local treatment:

- Radical cystectomy + lymphadenectomy with Bricker derivation or neobladder
- Bladder-preserving alternative in cT2N0: Tri modality treatment
  - Radiotherapy + weekly cisplatinum 40mg/m² (if cis-ineligible: gemcitabine 40mg/m² 2x/w)
  - TURB before and halfway through chemoradiotherapy
  - Exclusion criteria for TMT: Poor bladder function, associated carcinoma in situ, tumor in urethra/bladder neck/ostium, hydro-uretronephrosis, pt not motivated for cystoscopic follow up.
  - Offer neo-adjuvant chemotherapy, but strong recommendation is lacking

Inoperable MIBC (cN2-3 or inoperable cT4):

- Cisplatinum-gemcitabine or dd-MVAC, combined with nivolumab
- CT Tx-abdomen every 3 cycles
- In case of downstaging in fit pts: discuss radical cystectomy, considering the high risk of relapse

Adjuvant treatment:

- If pT3-4 or pN+
  - Without neo-adjuvant chemo and cisplatinum-eligible: 4x cis-gem or 6x dd-MVAC
  - After neo-adjuvant chemo or cisplatinum ineligible AND TPS ≥1%: 12x nivolumab
- Others: none.
- Radiotherapy only in selected cases
- Follow-up: CT Tx-abdomen every 3mo during adjuvant treatment

Special situations

- Unfit or refusing radical therapy: radiotherapy, if possible with concomitant chemotherapy, without curative intent.
- Pure squamous cell or adenocarcinoma: no (neo-)adjuvant chemotherapy.
- Small cell neuroendocrine histology: neo-adjuvant cisplatinum-etoposide followed by local therapy
- Based on case series suggesting benefit of immune checkpoint inhibitors in UCC with variant histology: consider adjuvant nivolumab if pT3-4 or pN+
- Urachal adenocarcinoma is treated as an intestinal malignancy, not urological
- T1 G3 micropapillary bladder UCC : cystectomy + lymphadenectomy

Follow-up after treatment with curative intent

- Organize via urology (incl after adjuvant treatment), to assess functional outcomes after surgery and tailored follow up of the remaining urinary tract.
- Standard: CT Tx-abdomen every 6mo in year 1-3 and every 12mo in year 4-5.
- After Tri modality treatment: cystoscopy with biopsies every 3mo year1-2, every 6mo year 3-4, every 12mo afterwards

Metastatic bladder cancer

1st line:

- Cisplatinum-eligible: 6x cisplatinum-gemcitabine + nivolumab (max 2yr)
- Consider split-dose if borderline cis-eligible
- Cis-ineligible, carboplatinum-eligible: 4-6x carboplatinum-gemcitabine, followed by avelumab maintenance in case of disease control
- Platinum-ineligible and CPS > 10 : pembrolizumab mono or best supportive care
- If oligometastatic (1-3 mets) and deep response on 1St line: consider discussing radical local treatment of bladder + SBRT of metastases
- If previous platinum and/or IO for localized MIBC: rechallenge if progression >12mo

2nd line:

- After chemo and IO: enfortumab-vedotin
- After chemo: pembrolizumab (regardless of CPS)
- Test for somatic FGFR2/3-alterations

After chemo, IO and enfortumab-vedotin

- Erdafitinib for FGFR2/3-alterated tumors after chemo and IO in metastatic MIBC: upon request of samples
- Rechallenge platinum-based chemotherapy if PD > 6m after stop
- Docetaxel, gemcitabine, paclitaxel

Keep in mind

- After radical cystectomy: elevated risk of metabolic acidosis (NaHCO3 substitution), vitamin B12 deficiency, urinary infections, ureter strictures, urolithiasis, kidney failure
- Bone metastases: Ca-vitD + denosumab
- PAC required for chemo and for enfortumab-vedotin (irritant)

What's new ?

- NMIBC: TAR is a device providing intra-vesical drug delivery with promising response rates in early trials with different drugs (erdafitinib, gemcitabin)
- MRI is highly accurate in distinguishing T1 from ≥T2 disease and assessing response to neo-adjuvant treatment.
- MIBC: neo-adjuvant cisplatinum-gemcitabin-durvalumab, followed by cystectomy and adjuvant durvalumab (Powles et al NEJM 2024, NIAGARA): pending reimbursement
- Cisplatinum split-dose allowed up to eGFR 40ml/min.
- MIBC: Approaches avoiding cystectomy, both with and without radiotherapy, are gaining ground.
- Metatstatic MIBC: enfortumab-vedotin + pembrolizumab as first line (Powles et al NEJM 2023, EV-302/KEYNOTE-A39): pending reimbursement

References

Leyderman, M., Chandrasekar, T., Grivas, P. *et al.* Metastasis development in non-muscle-invasive bladder cancer. *Nat Rev Urol* (2024).