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BLADDER CANCER (BC), BASICS

EPIDEMIOLOGY

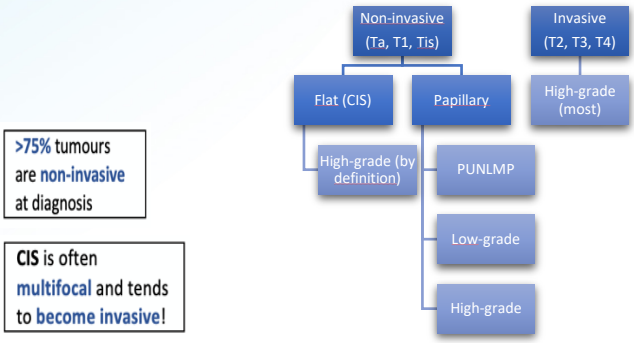
The **most common** tumour of the urinary tract
More frequent in **men** and **Caucasians**
4th for incidence and **8th for mortality** in American man
Maximum incidence **after 55 years**

WHO CLASSIFICATION 2016

- **Urothelial tumours (90%)**
- Squamous cell neoplasm
- Glandular neoplasm (e.g., adenocarcinoma)
- Neuroendocrine tumours (e.g., small cell carcinoma)
- Others: urachal carcinoma, tumours of Müllerian type, melanocytic tumours, mesenchymal tumours, haematopoietic and lymphoid tumours, miscellaneous tumours

RISK FACTORS	
SMOKING	**Most well-established risk factor** (causing 50-65% of male cases and 20-30% of female cases) Incidence is directly related to the **duration of smoking and the number of cigarettes** per day Decrease in the risk after **smoking cessation** (40% within one to four years, 60% after 25 years)
AROMATIC AMINES	**Occupational exposure** (dyes, rubbers, textiles, paints, leathers, chemicals) Risk significantly greater **after 10 years** or more of exposure Mean **latency period** usually exceeds **30 years**
SCHISTOSOMA HAEMATOBIUM	Second most common **parasitic infection** after malaria Endemic in some regions (e.g., **Egypt**) Related with **squamous cell carcinoma**
OTHERS	Familiarity, cyclophosphamide, pioglitazone, radiotherapy

GRADING AND STAGING



Grading and staging are the most important prognostic factors: **high-grade** and **muscle-invasive tumours** have the **worst prognosis**!

TNM 2017	
Tx	Primary tumour **cannot be assessed**
T0	No evidence of primary tumour
Ta	**Non-invasive papillary carcinoma**
Tis	**Carcinoma in situ (CIS)**
T1	Tumour invades **subepithelial connective tissue**
T2	**T2a** - Tumour invades **superficial muscle** (inner half) **T2b** - Tumour invades **deep muscle** (outer half)
T3	**T3a** - Tumour invades **perivesical tissue microscop.** **T3b** - Tumour invades **perivesical tissue macroscop.**
T4	**T4a** - Tumour invades **prostate stroma, seminal vesicles, uterus or vagina** **T4b** - Tumour invades **pelvic wall or abdominal wall**
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a **single lymph node in the true pelvis** (hypogastric, obturator, external iliac, or presacral)
N2	Metastasis in **multiple regional lymph nodes in the true pelvis** (hypogastric, obturator, external iliac, or presacral)
N3	Metastasis in **common iliac lymph node(s)**
M0	No distant metastasis
M1	**M1a** -**Non-regional lymph nodes** **M1b** -**Other distant metastases** (lungs, liver, bones)

CLINICAL PRESENTATION

MACROHAEMATURIA is the most frequent sign
ASSOCIATED STORAGE LUTS should suggest CIS
URINARY OBSTRUCTION and **PELVIC PAIN** may appear in advanced cases
Tumour may be **ASYMPTOMATIC** and accidentally diagnosed with ultrasound

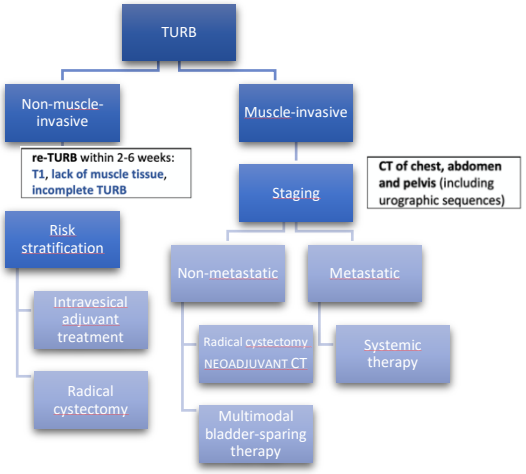
DIAGNOSIS

INSTRUMENTAL AND LABORATORY TESTS FOR DIAGNOSIS	
ULTRASOUND	**First level examination** in case of haematuria. **It cannot detect CIS**
CYSTOSCOPY	**Necessary** for the diagnosis. It **cannot be replaced** by any other non-invasive test. **Flexible cystoscopy** is preferable in men if available. A **comprehensive description of the tumour and the use of a bladder diagram are recommended.** **CIS** can present as a velvet-like, reddish area, indistinguishable from inflammation, or it may not be visible at all!
URINARY CYTOLOGY	Useful to detect **high-grade tumours** (e.g., CIS). **High sensitivity** in high-grade tumours (84%), but low sensitivity in low-grade tumours (16%). **Specificity exceeds 90%.** Three consecutive samples can increase sensitivity. **Paris system** for cytology reporting. Morning urine not suitable for cytolysis
CT UROGRAPHY	In selected cases (e.g., tumours located in the trigone, multiple- or high-risk tumours)

BIOPSY DURING CYSTOSCOPY

- **Abnormal-looking mucosa**
- **Normal-looking mucosa in selected cases** (positive cytology, history of HG tumours, tumours with non-papillary appearance). In these cases, **mapping biopsies** (trigone, bladder dome, right, left, anterior and posterior bladder wall) should be performed. **Fluorescence-guided (PDD) biopsies** should be performed if available.
- **Prostatic urethra in selected cases** (CIS is present or suspected, positive cytology without evidence of tumour in the bladder, visible abnormalities of the prostatic urethra). **Resection loop** should be used.

RISK STRATIFICATION
Low-risk: primary, solitary, Ta, PUNLMP or low-grade, <3cm
Intermediate-risk: non-low-risk, non-high-risk
High-risk: T1 or high-grade or CIS or Ta low-grade multiple recurrent large (>3cm)
Highest-risk: T1 high-grade + bladder CIS, T1 high-grade + CIS in prostatic urethra, T1 high-grade multiple and /or large and/or recurrent, some forms of variant histology, lymphovascular invasion



INTRAVESICAL ADJUVANT TREATMENT	Indicated for **non-muscle-invasive tumours to reduce recurrence rate (RR).** **Single instillation of Mitomycin C** reduces the RR in **low-risk** patients **Repeat Mitomycin C instillations** reduce the RR in **intermediate-risk** patients **Repeat BCG instillations** reduce the RR in **intermediate-risk and high-risk** patients. Three-year maintenance is more effective than one year to reduce RR in patients with high-risk tumours but not with intermediate-risk tumours
RADICAL CYSTECTOMY	Indicated for **T2-T4a, N0M0 tumours.** Do not defer more than **3 months.** Removal of **bladder, regional lymph nodes regional,** prostate and seminal vesicles in man, uterus ovaries and anterior part of the vagina in woman. **Continent or non-continent** urinary diversion (type of urinary diversion does not affect oncological outcomes). **RADICAL CYSTECTOMY: gold standard treatment**. Whether ORC or RARC, should be performed only in high-volume centres (at least 10, preferably > 20, RCs hospital/per year.) **NEOADJUVANT CISPLATIN-BASED COMBINATION THERAPY FOR T2-T4A, CN0M0 TUMOURS.** **ADJUVANT CISPLATIN-BASED COMBINATION THERAPY TO PATIENTS WITH PT3/4 AND/OR PN+ DISEASE IF NO NEOADJUVANT THERAPY WAS GIVEN.** Palliative purpose for patients with T4b tumours. Indicated for **NON-MUSCLE-INVASIVE TUMOURS IN SELECTED CASES** (BCG-refractory / unresponsive / relapsing tumours, highest-risk tumours)
MULTIMODAL BLADDER-SPARING THERAPY	**Alternative for patients with T2N0M0 tumour unfit for cystectomy.** In a highly selected patient population, long-term survival rates of multimodality treatment are comparable to those of early cystectomy. **TURB + RADIOTHERAPY + CHEMOTHERAPY**
SYSTEMIC THERAPY	**- FIRST-LINE TREATMENT FOR CISPLATIN-ELIGIBLE PATIENTS** Use **cisplatin**-containing combination chemotherapy with **GC, MVAC, preferably with G-CSF, HD-MVAC with G-CSF or PCG.** Do not offer carboplatin and non-platinum combination chemotherapy. **-FIRST-LINE TREATMENT IN PATIENTS INELIGIBLE (UNFIT) FOR CISPLATIN** Offer **checkpoint inhibitors pembrolizumab or atezolizumab to PD-L1-positive patients.** Offer **carboplatin combination chemotherapy if PD-L1 is negative.** **-SECOND-LINE TREATMENT** Offer **checkpoint inhibitor pembrolizumab to patients progressing during, or after, platinum-based combination chemotherapy** for metastatic disease. Alternatively, offer treatment within a **clinical trial** setting.

FOLLOW-UP

As a result of the risk of recurrence and progression, **non-muscle-invasive need for follow-up** after TURB
Duration: **5 years** (low-risk) or **lifetime** (intermediate-to-high risk)
First cystoscopy at 3 months is an important prognostic indicator

- Low-risk: **cystoscopy** (3 months from TURB, 9 months from previous cystoscopy, yearly until five years)
- Intermediate-risk: **individualized**
- High-risk: **cystoscopy** and **urinary cytology** (every 3 months for 2 years, every 6 months until five years, yearly) + **CT urography** (yearly)