EPIDEMIOLOGY AND AETIOLOGY:

Bladder cancer (BC) is the 7th most commonly diagnosed cancer in males. The worldwide age-standardised incidence rate (per 100,000 person/years) is 9.5 in men and 2.4 in women. Bladder cancer incidence and mortality rates vary across countries. Approximately 75% of patients with BC are non-muscle-invasive bladder carcinomas (NMIBC): disease confined to the urothelium (stage Ta), carcinoma in situ or lamina propria (stage T1).

Active and passive tobacco smoking is the main risk factor, accounting for approximately 50% of cases. Occupational exposure to aromatic amines, polycyclic aromatic hydrocarbons and chlorinated hydrocarbons is the second most important risk factor for BC, accounting for about 10% of all cases. The increased risk of developing bladder cancer in patients undergoing external-beam radiotherapy, brachytherapy, or a combination, must be considered during patient follow-up.

PATHOLOGICAL STAGING AND CLASSIFICATION SYSTEMS:

2017 TNM CLASSIFICATION OF URINARY BLADDER CANCER

T - Primary Tumour
T1 Tumour invades subepithelial connective tissue
T2 Tumour invades muscle
T1a Tumour invades superficial muscle (inner half)
T1b Tumour invades deep muscle (outer half)
T2a Tumour invades perivesical fat
T2b Tumour invades macroscopic (visceral) lymph nodes
T3a Tumour invades any of the following: prostate stroma, seminal vesicles, seminal vesicles, uterine, vagina, pelvic wall, abdominal wall
T3b Tumour invades prostate stroma, seminal vesicles, uterine, vagina, pelvic wall, abdominal wall
T4a Tumour invades deep pelvic veins
T4b Tumour invades pelvic or abdominal wall
N - Regional Lymph Nodes
N0 No regional lymph nodes present
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 nodes
M - Distant Metastases
M0 No distant metastasis
M1a Non-regional lymph nodes
M1b Other distant metastases

T1 subclassification: the depth and extent of invasion into the lamina propria has been demonstrated to be of prognostic value and its use is recommended by the most recent 2016 World Health Organization (WHO) classification.

-Carcinoma in situ (CIS) and its classification: CIS is a flat, HG, non-invasive urothelial carcinoma. It is often multifocal and can be missed or misinterpreted as an inflammatory lesion during cystoscopy.

From a clinical point of view, CIS may be classified as:
- Primary: CIS with no previous or concurrent papillary tumours and no previous CIS.
- Secondary: CIS during follow-up of patients with a previous not-CIS tumour.
- Concurrent: CIS in the presence of any other urothelial tumour in the bladder.

-Histological grading of NMIBC: NMIBC is classified according to the WHO 1973 (G1-G3) and/or the WHO 2004/2016 (PUNLMP, LG/HG) systems.

Both systems are prognostic for progression, but not for recurrence.

WHO 2004/2016 provides better reproducibility than the 1973 classification.

DIAGNOSIS:

- Patient history and physical examination: A focused patient history and urological examination are mandatory.
- Signs and symptoms: Haematuria is the most common finding in NMIBC. CIS might be suspected in patients with lower urinary tract symptoms.
- Imaging:
  - Use renal and bladder ultrasound and/or computed tomography-intravenous urography (CT-NM) during the initial work-up in patients with haematuria.
  - Once a bladder tumour has been detected, perform a CT urography in selected cases (e.g., tumours located in the trigone, multiple or high-risk tumours).
- Urinary molecular marker tests: Sensitivity is usually higher at the cost of lower specificity compared to urine cytology. Promising novel urinary biomarkers, assessing multiple targets, have been tested in prospective multicentre studies.
- Urinary cytology: high sensitivity in HG and G3 tumours (84%), but low sensitivity in LG/G1 tumours (16%). Cytology is useful, particularly as an adjunct to cystoscopy, in patients with HG/G3 tumours.
- Cystoscopy: Describe all macroscopic features of the tumour (site, size, number, and appearance) and mucosal abnormalities during cystoscopy. Use a bladder diagram.
- Transurethral resection of TaT1 bladder tumours: Transurethral resection of the bladder tumour (TURB) followed by pathology investigation of the obtained specimen(s) is an essential step in the management of NMIBC. TURB should be performed systematically in individual steps.

Take biopsies from abnormal-looking urothelium. Biopsies from normal-looking mucosa are recommended if cytology or urinary molecular marker test is positive. If the equipment is available, perform fluorescence-guided (FID) biopsies.

Take a biopsy of the prostate urethra in cases of bladder neck tumour. If bladder carcinoma in situ is present or suspected, if there is positive cytology or urinary molecular marker test without evidence of tumour in the bladder, or if abnormalities of the prostate urethra are visible. If biopsy is not performed during the initial procedure, it should be completed at the time of the second resection.

Take a prostate urethra biopsy from the pro-cocciolar area (between the 5 and 7 o'clock position) using a resection loop. In case any abnormal-looking areas in the prostatic urethra are present at this time, these need to be biopsied as well.

Use methods to improve tumour visualisation (fluorescence cystoscopy, narrow-band imaging) during TURB, if available.

In patients with positive cytology, but negative cystoscopy, exclude an upper tract urothelial carcinoma. CIS in the bladder by mapping biopsies or FID-guided biopsies and tumour in the prostatic urethra (by prostatic urethra biopsy).

Perform a second TURB in the following situations:
- if there is no detrusor muscle in the specimen after initial resection, with the exception of Ta/G1/G2 tumours and primary CIS;
- in T1 tumours.

If indicated, perform a second TURB within 2-4 weeks after the initial resection. This second TURB should include resection of the primary tumour site.

Register the pathology results of a second TURB as it reflects the quality of the initial resection.

Inform the pathologist of prior treatments (intravesical therapy, radiotherapy, etc.).

The pathological report should specify tumour location, tumour grade and stage, lymphovascular invasion, subtypes of urothelial carcinoma (variant histologies), presence of CIS and detrusor muscle.