

## Epidemiology, pathology and diagnosis

### EPIDEMIOLOGY AND AETIOLOGY:

Bladder cancer (BC) is the 7<sup>th</sup> most commonly diagnosed cancer in males. BC incidence and mortality rates vary across countries. For about 35% of patients, bladder cancer is either muscle-invasive or metastatic at disease presentation. Non-muscle invasive disease can progress to become muscle-invasive bladder cancer later on in the disease course.

Active and passive tobacco smoking is the main risk factor, while the exposure-related incidence is decreasing.

### PATHOLOGY:

Specimens should be taken from the superficial and deep areas and sent to the pathology laboratory separately.

All muscle-invasive bladder cancer (MIBC) cases are high-grade. Identification of morphological subtypes is important for prognostic reasons and treatment decisions.

### PATHOLOGY DIFFERENTIATIONS

1. Pure urothelial carcinoma (more than 90% of all cases);
2. Urothelial carcinomas with partial squamous and/or glandular or trophoblastic differentiation;
3. Micropapillary and microcystic UC;
4. Nested variant (including large nested variant);
5. Lymphoepithelioma-like;
6. Plasmocytoid, signet ring, diffuse;
7. Some UCs with small-cell carcinomas;
8. Sarcomatoid carcinomas;
9. Poorly differentiated.

Recommendations	Strength rating
Record the depth of invasion (categories pT2a and pT2b, pT3a and pT3b or pT4a and pT4b).	Strong
Record margins with special attention paid to the radial margin, prostate, ureter, urethra, peritoneal fat, uterus and vaginal top.	
Record the total number of lymph nodes (LNs), the number of positive LNs and extranodal spread.	
Record lymphatic or blood vessel invasion.	
Record the presence of carcinoma <i>in situ</i> .	

\*Most frequent non-urothelial carcinomas: Pure squamous cell carcinoma, Adenocarcinoma and Neuroendocrine tumors\*

### STAGING: TNM, 2017:

T - Primary Tumour	
Tx	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Ta	Non-invasive papillary carcinoma
Tis	Carcinoma <i>in situ</i> : "flat tumour"
T1	Tumour invades subepithelial connective tissue
T2	Tumour invades muscle
T2a	Tumour invades superficial muscle (inner half)
T2b	Tumour invades deep muscle (outer half)
T3	Tumour invades perivesical tissue:
T3a	microscopically
T3b	macroscopically (extravesical mass)
T4	Tumour invades any of the following: prostate stroma, seminal vesicles, uterus, vagina, pelvic wall, abdominal wall
T4a	Tumour invades prostate stroma, seminal vesicles, uterus, or vagina
T4b	Tumour invades pelvic wall or abdominal wall
N - Regional Lymph Nodes	
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 a common iliac lymph node(s)
M - Distant Metastasis	
M0	No distant metastasis
M1a	Non-regional lymph nodes
M1b	Other distant metastasis

### DIAGNOSIS:

- Symptoms: **Most common symptom: painless haematuria**
- Physical examination: **bimanual examination under anaesthesia should be carried out before and after TUR**
- Bladder imaging: **Patients with a bladder mass in any diagnostic imaging technique should undergo cystoscopy, biopsy and/or resection.**
- Cytology: **high sensitivity in high-grade urothelial tumours.**
- Cystoscopy, **transurethral resection of invasive bladder tumours:**

Recommendations	Strength rating
Describe all macroscopic features of the tumour (site, size, number and appearance) and mucosal abnormalities during cystoscopy. Use a bladder diagram.	Strong
Take a biopsy of the prostatic urethra in cases of bladder neck tumour, when bladder carcinoma <i>in situ</i> is present or suspected, when there is positive cytology without evidence of tumour in the bladder, or when abnormalities of the prostatic urethra are visible.	Strong
Take a biopsy at the time of the second resection, if no biopsy was taken during the initial procedure.	Strong
In women undergoing subsequent orthotopic neobladder construction, obtain procedural information (including histological evaluation) of the bladder neck and urethral margin, either prior to, or at the time of cystoscopy.	Strong
In the pathology report, specify the grade, depth of tumour invasion, and whether the lamina propria and muscle tissue are present in the specimen.	Strong

### -Imaging for staging of MIBC:

Summary of evidence	LE
Imaging as part of staging in muscle-invasive bladder cancer (MIBC) provides information about prognosis and assists in selection of the most appropriate treatment.	2b
There are currently insufficient data on the use of diffusion-weighted imaging (DWI) and <sup>18</sup> F-fluorodeoxyglucose-positron emission tomography/computed tomography (FDG-PET/CT) in MIBC to allow for a recommendation to be made.	
The diagnosis of upper tract urothelial carcinoma depends on CT urography and ureteroscopy.	2

Recommendations	Strength rating
In patients with confirmed MIBC, use computed tomography (CT) of the chest, abdomen and pelvis as the optimal form of staging.	Strong
Perform a CT urography for upper tract evaluation and for staging.	Strong
For upper tract evaluation, use diagnostic ureteroscopy and biopsy only in cases where additional information will impact treatment decisions.	Strong
Use magnetic resonance urography when CT urography is contraindicated for reasons related to contrast administration or radiation dose.	Strong
Use CT or magnetic resonance imaging (MRI) for staging locally advanced or metastatic disease in patients in whom radical treatment is considered.	Strong
Use CT to diagnose pulmonary metastases. Computed tomography and MRI are generally equivalent for diagnosing local disease and distant metastases in the abdomen.	Strong

-Comorbidity scales: **Chronological age is of limited relevance.**

**A comorbidity score developed in particular for the assessment of patients diagnosed with bladder cancer would be helpful.**

Recommendations	Strength rating
Base the decision on bladder-sparing treatment or radical cystectomy in elderly/frail patients with invasive bladder cancer on tumour stage and comorbidity.	Strong
Assess comorbidity by a validated score, such as the Charlson Comorbidity Index. The American Society of Anesthesiologists score should not be used in this setting (see Section 5.3.2).	Strong

### -Markers

**Currently, treatment decisions cannot be based on molecular markers.**

**In patients with metastatic disease, genetic profiling should always be done.**

**In invasive non metastatic disease, prospectively validated prognostic and predictive molecular biomarkers will present valuable adjuncts to clinical and pathological data.**