Etiology and diagnosis of bladder cancer

Introduction

• Incidence: the most common urothelial tumor, representing the 2nd most common urological tumor in men (4th in overall frequency) and the 1st in women (8th in overall frequency). It is more common in men (3:1), with a median age at diagnosis of 70 years.

• Race: more common in Caucasians than in African Americans, Latin Americans, or Asians. However, the mortality rate is higher among African Americans and women.

• UUT tumors develop in 2-4% of patients with bladder TCC, but the frequency increases if there is trigonal involvement (7.5%) or a high-grade tumor (up to 20%).

• Form of presentation of transitional cell carcinoma (TCC) of the bladder is:
  – Superficial or non-muscle invasive in 70% of cases.
  – Muscle-invasive in 20% of cases.
  – Metastatic in 10-15%.

Etiology

• Smoking: responsible for 50% of cases. The carcinogenic compounds found in tobacco are biphenyl amines. The risk is dose-dependent, with an HR 2-4 times higher than that of non-smokers. The latency period can be 15-20 years from the onset of exposure. The risk is twice as high in smokers of dark tobacco. The cessation of exposure reduces the risk, but it never disappears. Passive smokers are also at increased risk of developing bladder TCC.

• Environmental or occupational exposure: responsible for 20% of cases. It was the first described occupational cancer (exposure to aniline dyes). Associated with industrial jobs that entail exposure to aluminum, dyes, paints, petroleum, rubber, and textiles. Those most at risk are truck drivers, hairdressers, dry cleaners, printers, paper mill workers, plumbers and dental prostheses makers.

• Abuse of analgesics: especially phenacetins. Associated with a thickening of the basal membrane and papillary scarring (almost pathognomonic).

• Pelvic radiation.

• Chronic inflammation: chronic urinary tract infections associated with stones, catheters, and obstructions. Associated with squamous cell carcinoma or adenocarcinoma.

• Exposure to chemotherapy: the use of Cyclophosphamide leads to a 4-9-fold increase in RR.

• Genetic factors: non-hereditary familial association appears in 8% of cases, increasing the RR 2-fold compared to those with no familial association. The presence of polymorphisms in the detoxification mechanisms contributes to their high susceptibility to carcinogenic agents.

• Others: exposure to arsenic and ferns, Balkan nephropathy, intake of Aristolochia fangchi (slimming herb), and TCC of the UUT (15-75% develop metachronous or synchronous bladder tumors within 5 years).

Symptoms

• Hematuria (80-90% of cases): usually total, intermittent, monosymptomatic, and with clots. Can be:
  – Macroscopic (70-80%).
  – Microscopic (20%).

• Irritative voiding symptoms (20-30%): more common in high grade tumors (CIS) and invasive disease.

• Physical exam: the abdomen should be explored for abdominal masses. A DRE should be performed to rule out perivesical extension and the presence of inguinal or distant lymphadenopathies.
## Tumor, node, metastasis classification (TNM) (Fig 1)

### 2009 TNM classification of urinary bladder cancer

<table>
<thead>
<tr>
<th>Primary tumor</th>
<th>Lymph nodes</th>
<th>Distant metastast.</th>
</tr>
</thead>
<tbody>
<tr>
<td>$T_x$ Primary tumor cannot be assessed</td>
<td>$N_x$ Regional lymph nodes cannot be assessed</td>
<td>$M_x$ Distinct metastasis cannot be assessed</td>
</tr>
<tr>
<td>$T_0$ No evidence of primary tumor</td>
<td>$N_0$ No regional lymph node metastasis</td>
<td>$M_0$ No distant metastasis</td>
</tr>
<tr>
<td>$T_a$ Non-invasive papillary carcinoma</td>
<td>$N_1$ Metastasis in a single lymph node in the true pelvis (hypogastric, obturator, external iliac, or presacral)</td>
<td>$M_1$ Distinct metastasis</td>
</tr>
<tr>
<td>$T_{is}$ Carcinoma in situ “flat tumor”</td>
<td>$N_2$ Metastasis in multiple lymph nodes in the true pelvis (hypogastric, obturator, external iliac, or presacral)</td>
<td></td>
</tr>
<tr>
<td>$T_1$ Tumor invades subepithelial connective tissue</td>
<td>$N_3$ Metastasis in common iliac lymph node(s)</td>
<td></td>
</tr>
<tr>
<td>$T_2$ Tumor invades muscle</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$pT_{2a}$ Tumor invades superficial muscle (inner half)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$pT_{2b}$ Tumor invades deep muscle (outer half)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$T_3$ Tumor invades perivesical tissue</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$pT_{3a}$ Microscopically</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$pT_{3b}$ Macroscopically (extravesical mass)</td>
<td></td>
<td></td>
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<tr>
<td>$T_4$ Tumor invades any of the following: prostate, uterus, vagina, pelvic wall, abdominal wall</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$pT_{4a}$ Tumor invades prostate, uterus, or vagina</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$pT_{4b}$ Tumor invades pelvic wall or abdominal wall</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$N_x$ Regional lymph nodes cannot be assessed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$N_0$ No regional lymph node metastasis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$N_1$ Metastasis in a single lymph node in the true pelvis (hypogastric, obturator, external iliac, or presacral)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$N_2$ Metastasis in multiple lymph nodes in the true pelvis (hypogastric, obturator, external iliac, or presacral)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$N_3$ Metastasis in common iliac lymph node(s)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$M_x$ Distinct metastasis cannot be assessed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$M_0$ No distant metastasis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$M_1$ Distinct metastasis</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### TNM stage grouping

<table>
<thead>
<tr>
<th>Stage 0a</th>
<th>Stage 0is</th>
<th>Stage I</th>
<th>Stage II</th>
<th>Stage III</th>
<th>Stage IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>$T_3N_0M_0$</td>
<td>$T_1N_0M_0$</td>
<td>$T_1N_0M_0$</td>
<td>$T_{2a}N_0M_0 \text{ or } T_{2b}N_0M_0$</td>
<td>$T_{3a}N_0M_0, T_{3b}N_0M_0 \text{ or } T_{4a}N_0M_0$</td>
<td>$T_{4b}N_0M_0, T_{0-4}N_{1-3}M_0 \text{ or } T_{0-4}N_{1-3}M_1$</td>
</tr>
</tbody>
</table>

### 2004 WHO grading

<table>
<thead>
<tr>
<th>2004 WHO grading</th>
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</thead>
<tbody>
<tr>
<td>Papilloma</td>
</tr>
<tr>
<td>Papillary urothelial neoplasm of low malignant potential (PUNLMP)</td>
</tr>
<tr>
<td>Low grade papillary urothelial carcinoma</td>
</tr>
<tr>
<td>High grade papillary urothelial carcinoma</td>
</tr>
</tbody>
</table>
Fig 1. TNM classification. Primary tumor.

Pathology of bladder tumors

- **Malignant tumors:**
  - *Transitional cell carcinoma*: accounts for 90-95% of all bladder tumors. Associated with chronic infection, spinal cord injury, foreign bodies, and schistosomiasis.
  - *Squamous cell carcinoma*: accounts for 5% of bladder tumors. Associated with chronic infection, spinal cord injury, foreign bodies, and schistosomiasis.
  - *Adenocarcinoma*: accounts for 0.5-2% of cases. Associated with bladder extrophy, uretero-sigmoidostomy, and *infection or inflammation* of long duration. Its location is urachal or trigonal. If it does not originate in the *urachus*, a colorectal origin should be ruled out. The *signet ring* variant is very aggressive.
  - *Mixed variants*: transitional cell carcinoma associated with a squamous or glandular component (adenocarcinoma).
  - *Rare variants*:
    - *Micropapillary tumor*: aggressive variant that requires surgical excision.
    - *Carcinosarcoma*: aggressive variant with mixed components (epithelial and mesenchymal).
    - *Sarcomatoid carcinoma*: very aggressive variant consisting exclusively of epithelial cells.
    - *Small cell carcinoma*: may be pure or mixed, with positive immunohistochemical staining for *enolase*, *synaptophysin*, or *chromogranin*. The primary treatment of choice is systemic chemotherapy.
    - *Lymphoepithelioma-like cancer*: a rare variant with a better prognosis than transitional cell carcinoma.

- **Premalignant lesions:**
  - *Inverted papilloma*: benign lesion, although associated with synchronous or metachronous urothelial carcinoma.
  - *Leukoplakia*: squamous cell metaplasia with presence of *keratin*. Precursor of squamous cell carcinoma in 20% of cases.
• **Benign tumors:**
  - *Squamous cell metaplasia:* common lesion in 50% of women and 10% of men.
  - *Nephrogenic adenoma:* urothelial metaplasia secondary to trauma, infection, inflammation, or radiation. Associated with irritative voiding syndrome and hematuria. Treatment entails transurethral resection with subsequent follow-up cystoscopy.
  - *Pseudosarcoma:* associated with previous surgeries.
  - *Cystic or follicular cystopathy or malakoplasia.*

**Diagnosis**

- **Ultrasound:** constitutes the initial diagnostic test in most patients with hematuria. Detects UUT obstruction, the presence of renal masses, and bladder lesions.
- **IVP or uro-CT:** useful for assessing the presence of UUT obstruction or tumors. Uro-CT provides more information than the IVP, although the radiation received is greater.
- **Cystoscopy:** the diagnostic method of choice. Allows diagnosis and provides information on the size, number, and morphology (papillary, sessile, solid, presence of calcifications) of the tumors, as well as their basal characteristics and the presence of flat lesions (CIS). If a tumor has been correctly diagnosed with another technique, this can be omitted before transurethral resection.
- **Fluorescence cystoscopy:** entails the performance of a blue light cystoscopy after instillation of a photosensitizer (*hexaminolevulinic acid*). Has shown greater sensitivity in the detection of tumors, especially CIS, although with a high rate of false positives (inflammation, recent TUR, or endovesical instillation). Has a higher cost than conventional cystoscopy.
- **Urine cytology:** must be performed on fresh urine to ensure correct fixation. The first morning urine sample is not appropriate as cytolysis may be present. Its specificity is 95% with its sensitivity being directly related to tumor grade. High-grade tumors have a sensitivity >70% while for low-grade tumors it is 35-48%.
- **Urinary diagnostic markers:** there are various diagnostic urine tests, but none has replaced cystoscopy as a diagnostic tool. The tests are based on cytological analysis e.g. standard cytology, immunocytology, and fluorescence in situ hybridization (*FISH*), or fluid analysis, e.g. *BTA Trak*® (quantitative), *BTA Stat*® (qualitative), *NMP22*® (quantitative), and *Bladder Check*® (qualitative). They all have important limitations:
  - **Higher false positive rates** than standard cytology in the presence of hematuria, infection, or inflammation. FISH is positive before the appearance of the lesion.
  - **Their sensitivity** is higher than that of urine cytology, but they still fail to diagnose 20-40% of cases. Their specificity is lower than that of standard cytology.
  - **No test absolutely rules out** the presence of a tumor or avoids the need for cystoscopy. They have no proven usefulness in other non-transitional tumors.
  - **They can currently be used** together with cystoscopy, helping in the staging of tumors according to the risk of progression and recurrence.

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytology</td>
<td>35-70</td>
<td>94</td>
</tr>
<tr>
<td>BTA Stat®</td>
<td>58-70</td>
<td>73-75</td>
</tr>
<tr>
<td>BTA Trak®</td>
<td>69-71</td>
<td>65-66</td>
</tr>
<tr>
<td>Bladder Check®</td>
<td>50-56</td>
<td>86-87</td>
</tr>
<tr>
<td>NMP 22®</td>
<td>71-73</td>
<td>73-80</td>
</tr>
<tr>
<td>Immunocyt®</td>
<td>67-83</td>
<td>75-80</td>
</tr>
<tr>
<td>FISH</td>
<td>79-84</td>
<td>70-95</td>
</tr>
</tbody>
</table>

- **Abdominal-pelvic CT or abdominal-pelvic MRI with contrast:** useful in loco-regional and distant staging of muscle-invasive tumors.
- **Bone scan:** indicated to assess involvement of the bony framework.
- **Chest X-ray:** allows assessment of the pulmonary extent of the disease.
Initial treatment of bladder tumors

- The initial treatment of bladder tumors is the transurethral resection of the bladder lesion. The main considerations should be:
  - Laser electrocoagulation is not appropriate in primary tumors.
  - Cold biopsy resection and fulguration of the base and periphery is only indicated in small papillary recurrences.
  - The initial resection should include a sample of the detrusor muscle for appropriate staging of the tumor. The absence of this sample leads to understaging (>50%) for high grade stage I tumors.
  - Re-staging through a re-TUR is recommended between 2-6 weeks after the first resection in patients with T1 tumors, high grade tumors, multiple or large tumors, or when there is no muscle sample from the initial resection.

- Intra-diverticular tumor:
  - Tumor T0: if technically feasible, it can be resected safely.
  - Tumor T1 and particularly high grade tumors can be resected, although with a high risk of perforation. A partial cystectomy or a diverticulectomy should thus be considered as definitive options.

- Adjuvant treatment of the tumor depends on the pathology found in the sample (see chapter on Treatment of Non-muscle-invasive Bladder Tumors).