Treatment of non-muscle-invasive bladder cancer

Tumor, node, metastasis (TNM) classification

<table>
<thead>
<tr>
<th>2009 TNM classification of urinary bladder cancer</th>
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</thead>
<tbody>
<tr>
<td><strong>Primary tumor</strong></td>
</tr>
<tr>
<td>$T_x$</td>
</tr>
<tr>
<td>$T_0$</td>
</tr>
<tr>
<td>$T_a$</td>
</tr>
<tr>
<td>$T_{is}$</td>
</tr>
<tr>
<td>$T_1$</td>
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<table>
<thead>
<tr>
<th>TNM stage grouping</th>
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<tbody>
<tr>
<td>Stage 0$_a$</td>
</tr>
<tr>
<td>Stage 0$_{is}$</td>
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<tr>
<td>Stage 1</td>
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Pathology

- *$T_a$*: tumor confined to the mucosa.
- *$T_{is}$*: carcinoma *in situ*. A high-grade flat tumor confined to the mucosa; a precursor to invasive disease. Not susceptible to transurethral resection due to its multifocal nature and tendency to spread over the surface of the bladder.
- *$T_1$*: *lamina propria–invasive carcinoma* (submucosa). Its sub-classification based on the extent of invasion ($T_{1a}$, $T_{1b}$, $T_{1c}$) is controversial because of the lack of consistent limits, its low prognostic ability, and its inability to predict the response to intravesical treatment.
- **Presence of lymphovascular invasion**: associated with a poor prognosis, high probability of understaging, and poor survival rate.

Risk factors associated with recurrence and progression

<table>
<thead>
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<th>Risk factors associated with progression</th>
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<tr>
<td>Grade</td>
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<tr>
<td>Stage ($T_a$-$T_1$)</td>
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</tr>
<tr>
<td>Multifocality (single, 2-7 tumors, $\geq$8)</td>
<td>Concomitant CIS</td>
</tr>
<tr>
<td>Tumor size $\geq$3 cm</td>
<td>Tumor size $\geq$3 cm (in high grade)</td>
</tr>
<tr>
<td>Prior recurrence rate $\leq$1 year</td>
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<tr>
<td>Recurrence $\leq$3 months (strong predictor)</td>
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The combination of these factors allows for classification of non-muscle-invasive bladder tumors based on risk of progression and recurrence:

- **Low-risk tumors (50%)**:  
  - Solitary low grade papillary $T_a$ or $T_1$ tumors.  
  - 5-year progression rate $<5\%$.
- **Intermediate-risk tumors (35%)**:  
  - Recurrent low grade $T_a$-$T_1$ tumors.  
  - Multifocal low grade $T_a$-$T_1$ tumors.  
  - 5-year progression rate $<10\%$.
- **High-risk tumors (15%)**:  
  - High grade $T_a$-$T_1$ tumors or presence of CIS.  
  - 5-year progression rate is 25-50\% (> probability in multifocal $T_1G_3$ tumors and CIS).

Newer risk nomograms (like that of the EORTC) calculate risk on an individual basis.
Initial treatment of non-muscle-invasive bladder tumors

- Initial treatment of bladder tumors entails transurethral resection of the bladder lesion. The resection must be staged in different samples from the tumor, tumor base with muscle, and bladder fat, which must be analyzed separately. The goals of resection are to determine the histology, grade, and local staging of the tumor.
  - **Randomized biopsies:**
    - *Not indicated* in tumors that appear to be non-invasive papillary lesions with negative cytology and macroscopically normal bladder mucosa.
    - *Indicated* in tumors with positive cytology, including those appearing to be non-invasive papillary tumors with normal mucosa. Also indicated in muscle-invasive tumors when considering conservative treatment (partial cystectomy) to rule out CIS. Indicated in the presence of CIS-suggestive lesions in the bladder mucosa.
  - **Biopsy of the prostatic urethra:** a negative biopsy is associated with a negative apical urethral margin. Should be performed prior to a radical cystectomy, with a resection loop from the mid-prostate on both sides (at 5 and 7 o’clock) of the verumontanum due to the greater density of the prostatic ducts in this area. In women, bladder neck biopsies are performed instead of prostate biopsies.
  - **Re-TUR:** in cases of incomplete resection (no muscle) and high-grade T1 tumors.

Intravesical therapy

There are various intravesical adjuvant treatment options for decreasing the risk of recurrence after the initial resection of a tumor:

- **Single dose, immediate postoperative intravesical chemotherapy:**
  - **Technique:** endovesical instillation for 30-60 minutes in the first 6 hours after TUR. Ineffective if administered more than 24 h after surgery.
  - **Indications:**
    - Should be applied to all resected tumors that appear to be non-muscle invasive.
    - Indicated in low-risk and solitary tumors as a single adjuvant therapy.
    - Insufficient in intermediate- or high-risk tumors or multiple tumors; these require additional treatment.
  - **Chemotherapeutic agents:** principally Mitomycin C and Doxorubicin (Adriamycin). Others: Epirubicin, Gemcitabine, and Docetaxel (the latter two are in the research phase).

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<th>Dose</th>
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<td><em>Mitomycin C</em></td>
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<td>40 mg / 40 mL solution</td>
<td>30-60 min</td>
</tr>
<tr>
<td><em>Adriamycin</em></td>
<td>ADRIAMYCIN SOLUTION</td>
<td>50 mg / 25 mL solution</td>
<td>30-60 min</td>
</tr>
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- **Contraindications:** known allergy, bladder perforation, or excessive bleeding.
- **Toxicity:** *irritative voiding syndrome* in less than 5% of patients.
- **Results:** absolute rate of recurrence reduction over 3 years is approx. 12-15%.

- **Multidose delayed intravesical chemotherapy:**
  - **Technique:** treatment is initiated 1-4 weeks after TUR, once the pathological staging and grade has been determined. Instilled endovesically for 1-2 h a week for 6-8 weeks. Monthly maintenance therapy has no clear benefits. The following recommendations are for obtaining maximum benefits:
    - Decrease fluid intake several hours beforehand to reduce the formation of urine.
    - Empty the bladder before beginning instillation.
    - Alkalinize the urine to reduce acidic degradation.
  - **Indications:** intermediate-risk, papillary, and multifocal tumors, regardless of whether they have received single dose, immediate postoperative therapy.
  - **Chemotherapy agents:** principally Mitomycin C and Doxorubicin (Adriamycin). Others: Epirubicin, Gemcitabine, and Docetaxel (the latter two are in the research phase).
Multidose delayed intravesical chemotherapy

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- **Toxicity:**
  - Irritative voiding syndrome: 10-40%. More common with Mitomycin. Causes delays or abandonment of treatment in 5-10%.
  - Mitomycin: genital and palmar skin rash (10%).
  - Adriamycin: allergic reaction (1%).
- **Results:** absolute recurrence reduction rate over 3 years is approx. 12-15%, although results in the literature vary.
- **Limitations:** limited activity against CIS. Ineffective for failed BCG or other chemotherapy. Not effective in reducing the rate of progression.

**Immunotherapy with BCG (Calmette-Guerin bacillus):**

- **Technique:** initiated 2-6 weeks after TUR (81 mg are instilled into the bladder for 1-2 h a week for 6 weeks). Other protocols entail maintenance treatments for a minimum of 1 year (maximum=3 years). The scheme consists of 3-week miniseries in the first 3 months, then every 6 months for up to 3 years. The benefits of maintenance treatments have yet to be proven.

- **Indications:** high-risk tumors or in select cases of intermediate risk (previous failure of endovesical chemotherapy).
- **Contraindications:** traumatic catheterization, gross hematuria 24 h prior to instillation, urinary infection, active autoimmune disease, significant immunosuppression, known allergy, reflux, and history of treated TB.
- **Toxicity:**
  - Irritative voiding syndrome (>50%): accounts for 10% of treatment delays or abandonment. To reduce this side effect: use of anticholinergics, reduction of BCG dose, increasing instillation intervals to 2 weeks, reducing the duration of instillation, or oral administration of 400 mg Ofloxacin (SURNOX®) 8 and 20 h after instillation.
  - Flu-like symptoms (25%): the presence of fever >39.5° C for more than 24 h or recurrently may be a sign of BCG infection.
  - BCG infection/inflammation (5%): requires anti-TBC treatment for 3-6 months in moderately severe and severe cases. The treatment of choice is Isoniazide 300 mg/day + Pyridoxine 50 mg/day (CEMIDON® 300 B6) as a monotherapy for 3-6 months. Triple association is reserved for severe cases (see chapter on Genitourinary TB). Cycloserine and Pyrazinamide have proven ineffective in these cases. Additional application of oral or systemic corticosteroids helps reduce inflammatory effects.
  - Organ-specific manifestations: prostatitis (40% asymptomatic and 5% symptomatic), epididymitis (<2%), and distant organ involvement (<2%).
  - Allergic reactions (<5%): skin rash (2-5%), Reiter’s syndrome, polyarthritis.
  - Sepsis (<0.5%): the most common cause is traumatic catheterization. It has a rapid evolution with hypotension and cardio-vascular collapse. Early use of steroids along with antibiotic therapy can usually interrupt and block the inflammatory cascade.
Intravesical treatment according to risk of progression

Non-muscle-invasive bladder tumor

- **Low risk**: Single dose immediate postoperative
- **Intermediate risk**: Multidose delayed
- **High risk**: Single dose postoperative

- **Failure or selected cases**

### Indications for cystectomy (non-muscle-invasive TCC)

**Absolute indications:**
- **Unfavorable histology**: micropapillary carcinoma, small cell carcinoma, squamous cell carcinoma, or adenocarcinoma.
- **Incomplete resection** of a high-grade multifocal superficial tumor.
- **Recurrence of high-grade tumor** (pT1G3 or CIS) after failure of BCG (2 cycles).
- **Prostatic stromal invasion**.
- **Transitional high-grade carcinoma in bladder diverticulum**.
- **Bladder dysfunction with frequent tumor recurrence**.

**Relative indications:**
- **Recurrence of high-grade tumor** (pT1G3 or CIS) after one cycle of BCG.
- **Persistence of a high-grade tumor** in re-TUR (restaging).
- **Multifocal high-grade tumor** (T1G3) + CIS in the initial diagnosis.
- **Transitional carcinoma** with multiple recurrences in the prostatic urethra without stromal invasion.
Follow-up of superficial bladder tumors

Monitoring of patients is performed according to the risk of progression.

- **UUT study (IVP or uro-CT):**
  - *Low-risk tumor:* not indicated if the study was normal at the time of diagnosis.
  - *Intermediate-risk tumor:* every 1 or 2 years if multifocal or with frequent recurrences.
  - *High-risk tumor:* every 1 or 2 years.

- **Cystoscopy:**
  - *Low-risk tumor:* if cystoscopy at 3 months is negative, not repeated until 9 months from the first. From 12 months on, should be performed annually. If there is no recurrence within 5 years, the likelihood of recurrence is <5%.
  - *High-risk tumor:* cystoscopy recommended every 3 months for the first 2 years, every 4 months the 3rd year, every 6 months for the following 2 years, and then annually.
  - *Intermediate-risk tumor:* an intermediate pattern (between the first two) is followed.

- **Cytology:**
  - *Low-risk tumor:* not indicated if the initial cytology was negative.
  - *High-risk tumor:* every 3 months, with a pattern similar to that of cystoscopy.
  - *Intermediate-risk tumor:* with a pattern similar to that of cystoscopy.

- **Biopsy of bladder mucosa:**
  - *Macroscopic suspicious lesion.*
  - *Positive or suspicious cytology.*
  - *Evaluation of response to BCG treatment in the CIS.*

- **Laser electrocoagulation:**
  - *Indicated in small papillary recurrences* with a superficial appearance in previously diagnosed tumors with a low degree of progression.