MUSCLE-INVASIVE AND METASTATIC BLADDER CANCER

Recommendations from the EAU Working Party on Muscle-Invasive and Metastatic Bladder Cancer

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Introduction
The EAU Working Party on Muscle-invasive and Metastatic Bladder Cancer has published guidelines comprising risk factors, diagnostic workup, classification, treatment, quality of life and follow-up.

Most of the recommendations are based on the results of well conducted clinical studies. Due to the nature of the disease there are only few randomized trials or meta-analyses which can be considered for reference.

The recommendations of the working party concern transitional cell cancer (90% of all bladder carcinomas) invading muscle and beyond, as well as metastatic tumours.
**Table 1: TNM classification 2002**

**Urinary Bladder**

**T - Primary Tumour**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>TX</td>
<td>Primary tumour cannot be assessed</td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumour</td>
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<tr>
<td>Ta</td>
<td>Non-invasive papillary carcinoma</td>
</tr>
<tr>
<td>Tis</td>
<td>Carcinoma <em>in situ</em> (“flat tumour”)</td>
</tr>
<tr>
<td>T1</td>
<td>Tumour invades subepithelial connective tissue</td>
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<tr>
<td>T2</td>
<td>Tumour invades muscle</td>
</tr>
<tr>
<td>T2a</td>
<td>Tumour invades superficial muscle (inner half)</td>
</tr>
<tr>
<td>T2b</td>
<td>Tumour invades deep muscle (outer half)</td>
</tr>
<tr>
<td>T3</td>
<td>Tumour invades perivesical tissue</td>
</tr>
<tr>
<td>T3a</td>
<td>microscopically</td>
</tr>
<tr>
<td>T3b</td>
<td>macroscopically (extravesical mass)</td>
</tr>
<tr>
<td>T4</td>
<td>Tumour invades any of the following: prostate, uterus, vagina, pelvic wall, abdominal wall</td>
</tr>
<tr>
<td>T4a</td>
<td>Tumour invades prostate, uterus or vagina</td>
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<tr>
<td>T4b</td>
<td>Tumour invades pelvic or abdominal wall</td>
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**N - Regional Lymph Nodes**

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<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>NX</td>
<td>Regional lymph nodes cannot be assessed</td>
</tr>
<tr>
<td>N0</td>
<td>No regional lymph node metastasis</td>
</tr>
<tr>
<td>N1</td>
<td>Metastasis in a single lymph node 2 cm or less in greatest dimension</td>
</tr>
<tr>
<td>N2</td>
<td>Metastasis in a single lymph node more than 2 cm but not more than 5 cm in greatest dimension, or multiple lymph nodes, none more than 5 cm in greatest dimension</td>
</tr>
<tr>
<td>N3</td>
<td>Metastasis in a lymph node more than 5 cm in greatest dimension</td>
</tr>
</tbody>
</table>
Muscle-invasive and Metastatic Bladder Cancer

M - Distant Metastasis
- MX: Distant metastasis cannot be assessed
- M0: No distant metastasis
- M1: Distant metastasis

Histological Grading (WHO and International Pathology Consensus Committee, 1988)
- GX: Grading of differentiation cannot be assessed
- G1: Well differentiated
- G2: Moderately differentiated
- G3-4: Poorly differentiated/undifferentiated

No cases of papillary urothelial neoplasms of low malignant potential and low-grade cancer are present in muscle invasive tumours. However, morphological subtypes may be of importance for prognosis and treatment decisions:
- small-cell carcinomas
- transitional cell carcinoma with squamous, glandular or trophoblastic differentiation
- spindle cell carcinoma.

Diagnosis and Staging
TUR and bimanual palpation are the essentials for the assessment of the local tumour. Superficial and deep areas of the tumour have to be sent separately for pathohistological examination. CT or MRI are helpful to monitor patients undergoing neo-adjuvant chemotherapy or bladder sparing treatment. Lymphadenectomy of the pelvic lymph nodes is the only method to accurately assess lymph node involvement.
**Recommendations for diagnosis and staging:**

**mandatory clinical evaluations**
- TUR and bimanual examination.
- Biopsy of tumour base, prostatic urethra and bladder neck.
- Chest-X-ray.
- IVP or sonography.

**mandatory pathological evaluations**
- Depth of invasion.
- Assessment of margins.
- Histological subtyping.
- Extensive lymph node representation.

**Treatment of local tumour**
- Radical cystectomy with resection of the lymph nodes within the true pelvis up to the bifurcation of the iliac vessels is the standard of care for muscle-invasive tumours (T2-T4a,N0, M0).
- Radiotherapy with or without concomitant chemotherapy as well as bladder sparing surgery together with neoadjuvant and adjuvant chemotherapy may be considered as reasonable alternatives in special situations.
- Salvage cystectomy can be attempted in the case of persistenent disease. Performance status, co-morbidity and age can influence the choice of therapy. In radical cystectomy the bladder, as well as neighbouring organs, such as the prostate, seminal vesicles, uterus, part of the vagina and adnexa, is removed. The urethra can be preserved in case the margins are negative. The extent of lymphadenectomy is currently under discussion favouring the extended type including lymph nodes as far as the aortic bifurcation.
• Neoadjuvant chemotherapy with radical cystectomy has provided only a minimal benefit.
• Trials on adjuvant chemotherapy in high risk patients (T3-T4) or metastases to the lymph nodes provide controversial results and therefore the decision for the individual patient should be based on knowledge of the relapse rate per pathological stage.

**Recommendations for treatment of local tumour:**
• Radical cystectomy in T2-T4a, N0,M0.
• Radiotherapy with or without chemotherapy for bladder preservation or advanced stage T4b or significant co-morbidity.
• Palliative radiotherapy for uncontrollable local symptoms.
• Adjuvant chemotherapy in individual patients.

**Treatment of metastatic disease**
Systemic chemotherapy in patients with metastatic transitional cell carcinoma can induce tumour remission in as much as 70% of patients. However, cure is rarely obtained. Prognostic factors that predict response to chemotherapy include alkaline phosphatase, age greater than 60 years, performance status and visceral metastasis. Up-front chemotherapy with secondary surgery in case of remission can be considered.

Modern polychemotherapy protocols include cisplatin, gemcitabine, vinblastine, methotrexate and Taxol.
**Recommendation for treatment of metastatic disease**
- Cisplatin-containing polychemotherapy in metastatic disease with favourable prognosis.

**Urinary diversion after radical cystectomy**

Four treatment options are presently considered. Ileal conduit, orthotopic bladder substitution, continent reservoir and ureterosigmoidostomy. Each has specific advantages and disadvantages. Bladder substitution is the first option in many centres. The overall long-term outcome in terms of quality of life is good, and social, physical and functional activities are only moderately impaired.

Contraindications for more complex procedures are debilitating neurological or psychiatric illness, short life expectancy and impaired liver and renal function.

Contraindications for orthotopic bladder substitution are TCC of the prostatic urethra or bladder neck (female), widespread Tis, high-dose preoperative irradiation, complex urethral stricture and pre-existing incontinence (female).

**Recommendations for urinary diversion after radical cystectomy**
- Patients planned for cystectomy should be informed of the possible types of urinary diversions.
- The final decision has to be based on a consensus between patient and surgeon.
**Follow-up after treatment with curative intent**

Follow-up of patients with invasive bladder cancer after cystectomy or bladder preservation is recommended to detect local recurrence or distant metastases as early as possible to permit additional treatment when indicated and if possible.

**Recommendations for follow-up after treatment with curative intent**

*After cystectomy (intervals of 3 to 4 months)*
- physical examination, urine analysis, serum creatinine and blood gas analysis, sonography of abdomen, chest X-ray.
- barbotage of remaining urethra, assessment of upper urinary tract in case of pTis, CT of abdomen and bone scan in N+ patients.

*After radiotherapy*
- cystoscopy, urine cytology, CT of pelvis, sonography of abdomen, chest X-ray.

*This short booklet text is based on the more comprehensive EAU guidelines (ISBN 90-70244-27-6), available to all members of the European Association of Urology at their website - http://www.uroweb.org.*