



MUSCLE-INVASIVE AND METASTATIC BLADDER CANCER

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Introduction

Publications concerning muscle-invasive and metastatic bladder cancer are mostly based on retrospective analysis, including some larger multicentre studies and well-designed controlled studies. The studies underpinning the current guidelines were identified through a systematic literature research using Medline, the Cochrane central register of systematic reviews, and reference lists in publications and review articles. Due to the nature of the disease and the fact that treatment decisions rely on multiple factors, only a few randomized studies are available, so that it is difficult to obtain high-level evidence-based data for many recommendations.

It has to be emphasized that the current guideline contains information for the treatment of an individual patient according to a standardized approach. New data will promote constant re-evaluation of this document by an EAU expert panel in the years to come.

Three levels of recommendations are used:

The principal recommendations are marked in three grades (A-C), depending on the evidence source upon which a recommendation is based. Page 3 of this publication may be consulted for reference.

Staging system

The UICC 2002 TNM (Tumour, Nodes, Metastasis Classification) is used for staging (Table 1).

Table 1: 2002 TNM classification of urinary bladder cancer

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, uterus, vagina, pelvic wall, abdominal wall
T4a	Tumour invades prostate, uterus or vagina
T4b	Tumour invades pelvic or abdominal wall

N - Regional Lymph Nodes

NX	Regional lymph nodes cannot be assessed
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N0	No regional lymph node metastasis
N1	Metastasis in a single lymph node 2 cm or less in greatest dimension
N2	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
N3	Metastasis in a lymph node more than 5 cm in greatest dimension
M - Distant Metastasis	
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

Table 2: WHO grading 1973 and 2004

(Both classifications are used for the current guidelines since most of the retrospective studies were based on the old WHO 1973 grading system).

1973 WHO grading

- Urothelial papilloma
- Grade 1: well differentiated
- Grade 2: moderately differentiated
- Grade 3: poorly differentiated

2004 WHO grading

- Urothelial papilloma
- Papillary urothelial neoplasm of low malignant potential (PUNLMP)
- Low-grade papillary urothelial carcinoma
- High-grade papillary urothelial carcinoma

The following histological subtypes are more or less common in invasive bladder cancer:

- Urothelial carcinoma (more than 90% of all cases, usually high-grade)
- Squamous cell carcinoma
- Adenocarcinoma
- Transitional cell carcinomas with squamous, glandular or trophoblastic differentiation
- Small cell carcinoma (extremely rare)
- Spindle cell carcinoma (extremely rare).

Table 3: Recommendations for diagnosis and staging

Recommendations for primary assessment of presumably invasive bladder tumours:

- Renal and bladder ultrasonography, IVU or CT prior to TUR (Grade of recommendation: B).
- Cystoscopy with description of the tumour (site, size, number and appearance) and mucosal abnormalities. A bladder diagram is recommended (Grade of recommendation: C).
- TUR including detrusor muscle
- Biopsies of abnormal-looking urothelium.
- Biopsy of the prostatic urethra in case of bladder neck tumour, when bladder CIS is present or suspected or when abnormalities of prostatic urethra are visible (Grade of recommendation: C).
- Careful inspection with histological evaluation of the bladder neck and urethral margin, either prior to or at the time of cystectomy in women undergoing a subsequent orthotopic neobladder (Grade of recommendation: C).

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- The pathological report should specify the grade, the depth of tumour invasion and whether muscle tissue is present in the specimen (Grade of recommendation: C).

IVU = intravenous urography; CT = computed tomography; TUR = transurethral resection; PDD = photodynamic diagnosis

Recommendations for staging:

- For optimal local staging, either MR imaging with fast dynamic contrast-enhancement or MDCT with contrast enhancement are recommended for patients considered suitable for radical treatment (Grade of recommendation: B).
- For patients with confirmed muscle-invasive bladder cancer, MDCT of the chest, abdomen and pelvis is the optimal form of staging including MDCT urography for complete examination of the upper urinary tracts. If MDCT is not available, lesser alternatives are excretory urography and a chest X-ray (Grade of recommendation: B).

MR = magnetic resonance; MDCT = multidetector-row computed tomography

Treatment Failure of Non-Muscle Invasive Bladder Tumours

Recommendations

- In all T1 tumours considered for conservative treatment, a second TUR is recommended before deciding on definite treatment (Grade of recommendation: B).
- In all T1 tumours at high risk of progression (such as: high grade, multifocality, CIS present, tumour size; as outlined in the non-muscle-invasive bladder cancer guideline), immediate radical cystectomy is an option (Grade of recommendation: B).
- In all T1 patients failing intravesical therapy, cystectomy is an option. Delay in cystectomy increases the risk of progression and cancer-specific death (Grade of recommendation: B).

TUR = transurethral resection

Neoadjuvant Chemotherapy

Neoadjuvant cisplatin-containing combination chemotherapy improves overall survival by 5-7% at 5 years (Level of evidence: 1a), irrespective of the type of definitive treatment. It has its limitations regarding patient selection, current development of surgical technique, and current chemotherapy combinations.



Recommendations

- Neoadjuvant cisplatin-containing combination chemotherapy should be considered in muscle-invasive bladder cancer irrespective of definitive treatment (Grade of recommendation: A).
- Neoadjuvant chemotherapy is not recommended in patients with PS \geq 2 and impaired renal function (Grade of recommendation: B).

Radical Surgery and Urinary Diversion

Cystectomy is the preferred curative treatment for localised bladder neoplasms (Level of evidence: 3).

- Radical cystectomy includes removal of regional lymph nodes, the extent of which has not been sufficiently defined (Level of evidence: 3).
- Radical cystectomy in both sexes must not include the removal of the entire urethra in all cases, which may then serve as outlet for an orthotopic bladder substitution (Level of evidence: 3).
- Terminal ileum and colon are the intestinal segments of choice for urinary diversion (Level of evidence: 3).
- The type of urinary diversion does not affect oncological outcome (Level of evidence: 3).

Contraindications for orthotopic bladder substitution are positive margins at the level of urethral dissection, positive margins anywhere on the bladder specimen (in both sexes), if the primary tumour is located at the bladder neck or in the urethra (in women), or if tumour extensively infiltrates the prostate.

Recommendations

- Radical cystectomy is the treatment of choice in T2-T4a, N0-NX, M0, and high risk non-muscle invasive BC as outlined above (Grade of recommendation: B).
- Preoperative radiotherapy has shown no proven survival benefit and is not recommended (Grade of recommendation: A).
- Lymph node dissection should be an integral part of cystectomy; the extent of the lymphadenectomy in patients undergoing surgery with curative intent has not yet been precisely defined. (Grade of recommendation: B).
- Preservation of the urethra is reasonable if margins are negative. If no bladder substitution is attached, the urethra must be checked regularly (Grade of recommendation: B).
- Laparoscopic and robot-assisted laparoscopic cystectomy may be an option. Current data, however, have not sufficiently proven its advantages or disadvantages (Grade of recommendation: C).



Recommendations for urinary diversion

- Treatment is recommended at centres experienced in major types of diversion techniques and post-operative care (Grade of recommendation: B).
- Before cystectomy, the patient should be counselled adequately regarding all possible alternatives, and the final decision should be based on a consensus between patient and surgeon (Grade of recommendation: B).
- An orthotopic bladder substitute should be offered to male and female patients lacking any contraindications and who have no tumour in the urethra and at the level of urethral dissection (Grade of recommendation: B).

Palliative Cystectomy for Muscle-Invasive Bladder Carcinoma

Primary radical cystectomy in T4b bladder cancer is not a curative option. If there are symptoms, radical cystectomy may be a therapeutic/palliative option. Intestinal or non-intestinal forms of urinary diversion can be used with or without palliative cystectomy.

Recommendations

- For patients with inoperable locally advanced tumours (T4b), primary radical cystectomy is not a curative option (Grade of recommendation: B).
- The indication for performing a palliative cystectomy is symptom relief.
- Morbidity of surgery and quality of life should be weighed against other options (Level of evidence: 3; Grade of recommendation: B/C).

Neo-Adjuvant Radiotherapy in Muscle-Invasive Bladder Cancer

It is not proven that pre-operative radiotherapy for operable muscle-invasive bladder cancer increases survival (Level of evidence: 2). It is shown that pre-operative radiotherapy for operable muscle-invasive bladder cancer, using a dose of 45-50 Gy in fractions of 1.8-2 Gy results in down-staging after 4-6 weeks (Level of evidence: 2). Pre-operative radiotherapy with a dose of 45-50 Gy/1.8-2 Gy does not seem to significantly increase toxicity after surgery (Level of evidence: 3). There are suggestions in older literature that pre-operative radiotherapy will result in a decrease in local recurrence of muscle-invasive bladder cancer (Level of evidence: 3).

Recommendations

- Pre-operative radiotherapy is not recommended to improve survival (Grade of recommendation: B).
- Pre-operative radiotherapy for operable muscle-invasive bladder cancer results in tumour down-staging after 4-6 weeks (Grade of recommendation: A/B).

Bladder-Sparing Treatments

External beam radiotherapy

External beam radiotherapy alone should only be considered as a therapeutic option when the patient is unfit for cystectomy or a multimodality bladder-preserving approach (Level of evidence: 3). Radiotherapy can also be used to stop bleeding from the tumour when local control cannot be achieved by transurethral manipulation because of extensive local tumour growth (Level of evidence: 3).

Chemotherapy

Although cisplatin-based chemotherapy, as primary therapy for locally advanced tumours in highly selected patients, has led to complete and partial local responses, the long-term success rate is low (Level of evidence: 2b).

Multimodality treatment

There are comparable long-term survival rates in cases of multimodality treatment success. Delay in surgical therapy can compromise survival rates (Level of evidence: 2b).

Recommendations

- TUR alone is not a curative treatment option in most patients (Grade of recommendation: B).
- Radiotherapy alone is less effective than surgery (Grade of recommendation: B).
- Chemotherapy alone is not recommended as primary therapy for localized bladder cancer (Grade of recommendation: B).
- Multimodality treatment is an alternative in selected, well-informed and compliant patients where cystectomy is not considered for clinical or personal reasons (Grade of recommendation: B).

Adjuvant Chemotherapy

Adjuvant chemotherapy is under debate. Neither randomized trials nor a meta-analysis have provided sufficient data to support the routine use of adjuvant chemotherapy (Level of evidence: 1a).

Recommendation

Adjuvant chemotherapy is advised within clinical trials, but not for routine use because it has not been studied sufficiently (Grade of recommendation: A).

Metastatic Disease

Urothelial carcinoma is a chemosensitive tumour. Performance status and the presence or absence of visceral metastases are independent prognostic factors for survival. These factors are at least as important as the type of chemotherapy administered (Level of evidence: 3). Cisplatin-containing combination chemotherapy is able to achieve a median survival of up to 14 months, with long-term disease-free survival reported in about 15% of patients with nodal disease and good PS (Level of evidence: 1b). Single-agent chemotherapy provides low response rates of usually short duration (Level of evidence: 2a). Post-chemotherapy surgery after a partial or complete response may contribute to long-term disease-free survival (Level of evidence: 3).



Recommendations

- Prognostic factors guide treatment selection (Grade of recommendation: B).
- First-line treatment for fit patients: use cisplatin-containing combination chemotherapy with GC, MVAC, preferably with GCSF, or HD-MVAC with GCSF (Grade of recommendation: A).
- Carboplatin and non-platinum combination chemotherapy as first-line treatment in patients fit for cisplatin is not recommended (Grade of recommendation: B).
- First-line treatment in patients unfit for cisplatin: use carboplatin combination chemotherapy or single agents (Grade of recommendation: C).
- Second-line treatment: consider single agents or paclitaxel/gemcitabine if the patient has a good PS (Grade of recommendation: C).

Recommendations for general follow-up

Follow-up is based on the stage of initial tumour after cystectomy. At every visit, the following should be performed:

- history
- physical examination
- bone scan only when indicated.

Tables have been set up (see EAU Guidelines 2008 version, which are based on expert opinion and do not include non-oncological follow-up). They comprise a minimum set of tests that must be performed during follow-up (Grade of recommendation: C; Level of evidence: 4). After 5 years of follow-up,

stop oncological surveillance and continue with functional surveillance.



This short booklet text is based on the more comprehensive EAU guidelines (ISBN 978-90-70244-91-0), available to all members of the European Association of Urology at their website - <http://www.uroweb.org>.