clinical practice guidelines

Bladder cancer: ESMO Practice Guidelines for diagnosis, treatment and follow-up

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ingidence

The crude incidence of invasive bladder cancer in the European Union is 19.5/100 000/year, the mortality is 7.9/100 000/year; 70% of patients with bladder cancer are >65 years of age.

diagnosis

Pathological diagnosis should be made according to the WHO classification (Table 1) from a biopsy obtained by transurethral resection (TUR) of the primary tumour. Tumours should be graded as high and low grade according to latest WHO criteria and can concomitantly be graded according to the 1973 classification of high, low and intermediate grade carcinoma. Ninety per cent of bladder carcinomas are transitional cell carcinomas.

staging and risk assessment

Complete history and physical examination, blood counts, creatinine, chest X-ray (or CT), CT scan of the abdomen and pelvis and urine cytology. Additional diagnostic tests, such as bone scan, should be performed if clinically indicated.

Cystoscopic examination and TUR with a bimanual examination under anaesthesia should be undergone following a standarized protocol. Apart from biopsy and determination of number of tumours, size and the presence of extravesical extension or invasion of adjacent organs should be documented. Ideally both the base of the tumour and the tumour edges should be sent separately to the pathologist to ensure the presence of lamina propria and muscle in the specimen and aid an accurate staging. Because associated carcinoma in situ (CIS) has been shown to be an adverse prognostic factor, bladder biopsies should be taken from reddish suspicious areas when present or random biopsies from normal looking urothelium if there is a positive cytology or a previous diagnosis of associated CIS. Similarly, biopsies from the prostatic urethra should be taken if the tumour is located at the trigone or bladder neck area or when there is no bladder tumour and the procedure is performed to study a positive cytology, since the tumour could be located in the urothelium lining the prostatic urethra or the ductus. Management of bladder cancer is based on the pathologic findings of the biopsy, with attention to histology, grade and depth of invasion. Risk stratification should be used for non-muscle invasive bladder cancer (NMIBC) according to number, grade and history of previous tumours (Table 2a). Muscle-invasive bladder cancer (MIBC) should be staged according to the TNM system and grouped into categories (Table 2b).

treatment of non-muscle invasive bladder cancer (stage I disease)

Complete TUR is the treatment of choice for any initial bladder tumour. TUR should be followed by a single installation in the low-risk tumours, by multiple chemotherapeutic instillations in the intermediate-risk group and by bacille Calmette–Guerin (BCG) in the high-risk group. A second TUR is a reasonable option in high-risk NMIBC tumours either before intravesical therapy [II, B] or thereafter [III, B]. In case of T1 or high-grade T1 failing BCG, cystectomy should be considered due to the high risk of progression [III, B].

treatment of muscle invasive bladder cancer (stage II and III disease)

Radical cystectomy with extended lymphadenectomy is the standard treatment. Extended lymphadenectomy has been shown to be beneficial [III A], and may be curative in patients with metastasis or micrometastasis to a few nodes. Reconstruction may be performed either by ileal conduit or bladder replacement depending on tumour characteristics and patients choice.

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Conflict of interest: Dr Bellmunt has reported that he has a Consultant or Advisory Role for Eli Lilly (C), Pierre Fabre (U) and Sanofi Aventis (C); Dr Orsola, Dr Maldonado and Dr Kataja have reported no conflicts of interest.

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Table 1. WHO/ISUP 1998 Consensus WHO, 2004

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<tr>
<td><strong>Urothelial papilloma</strong></td>
<td>Papillary urothelial neoplasm of low malignant potential (PUNLMP)</td>
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<tr>
<td><strong>Urothelial carcinoma low grade</strong></td>
<td>Urothelial carcinoma high grade</td>
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Table 2a. Risk classification of NMIBC; adapted from EAU Guidelines

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<tr>
<th>Low risk</th>
<th>Intermediate risk</th>
<th>High risk</th>
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<tbody>
<tr>
<td>Initial, low-grade, ≤3 cm tumor</td>
<td>Low-grade recurrent, multiple or &gt;3 cm tumor</td>
<td>Any high-grade non-muscle invasive tumor or CIS</td>
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Table 2b. TNM staging system

<table>
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<th>NMIBC or stage I; T1 N0 M0</th>
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<tr>
<td>MIBC</td>
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<tr>
<td>Stage II T2a–T2b N0 M0</td>
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<tr>
<td>Stage III T3a–T3b, T4a N0 M0</td>
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Locally advanced or metastatic bladder cancer or stage IV; T4b N0 M0, any T N1–N3 M0, any T any N M1


External beam radiotherapy alone should only be considered as a therapeutic option when the patient is unfit for cystectomy or for a multimodality bladder-preserving approach [III]. External beam radiotherapy should be delivered with 3D conformal radiation therapy or intensity-modulated radiation therapy (IMRT) techniques.

Two large randomized trials and a meta-analysis support the use of neoadjuvant chemotherapy before cystectomy for T2 and T3 disease. The demonstrated survival benefit encourages the use of platinum-based combination chemotherapy before radical cystectomy or definitive radiotherapy [I, A]. Available trials provide insufficient evidence for the routine use of adjuvant chemotherapy in clinical practice [I, A]. However, based on retrospective studies showing some benefit of adjuvant chemotherapy in node-positive patients, this additional treatment may be considered in this context.

Bladder-preserving approaches, with a complete TUR and radiotherapy alone or with concomitant chemotherapy, are alternatives to cystectomy for patients who are medically unfit for surgery or unwilling to undergo cystectomy [II, A]. Concurrent cisplatinum plus radiotherapy is the most common chemoradiation method. If no residual tumour after pelvic examination and biopsy (pT0) is present, an additional boost to the surgical bed is recommended. Up to 70% of the patients are free of tumour after the first cystoscopy control. However, during follow-up, one-quarter of these individuals developed a new lesion requiring additional treatment.

The ideal patient for a bladder-preserving approach is one with an initial T2 tumour, ≤5 cm, no CIS, pT0 after a second TURBT, with no hydronephrosis, good performance status (PS) and with a proper bladder capacity and function [II, A]. In both cases, post-procedure TUR is recommended in order to ensure response and to restage the tumour.

Treatment of metastatic bladder cancer (stage IV disease)

Platinum-based combination chemotherapy with methotrexate–vinblastine–doxorubicin–cisplatinum (M-VAC) or gemcitabine–cisplatinum (GC) prolongs survival [I, A]. The addition of a third agent (paclitaxel) to gemcitabine–cisplatinum has been demonstrated to be of benefit in only a subset of patients having the bladder as the primary origin of the disease [I, B], and should be considered investigational.

Patients unfit for cisplatin-based chemotherapy may be palliated with a carboplatin-based regimen or single-agent taxane or gemcitabine. Patients with PS 2 and poor renal function have very limited benefit when receiving chemotherapy and new strategies for these patients are needed [II, A].

Selected patients with locally advanced disease (T4b N1) may be candidates for cystectomy and lymph node dissection or definitive radiotherapy following systemic therapy.

The role of antiangiogenic therapy is investigational in first- and second-line therapy. Vinflunine appears as an option for second-line therapy in patients progressing to first-line platinum-based chemotherapy [I, B] producing a survival benefit in eligible patients.

Palliative radiotherapy may be used to reduce symptoms such as pain or bleeding. The role of consolidative radiation therapy after chemotherapy in patients with loco-regional relapses is under evaluation [III, B].

Response evaluation

Response evaluation with cystoscopy and cytology is mandatory following BCG treatment and in patients after a bladder-preservation strategy. Response evaluation during chemotherapy with the initial radiographic tests is necessary.

Follow-up

There is no generally accepted follow-up protocol and therefore the possible alternatives could be as follows. Patients treated with a bladder-preservation strategy, cystoscopy and urinary cytology every 3 months during the first 2 years, and every 6 months thereafter. After cystectomy, clinical control every 3 months during the first 2 years and subsequently every 6 months for 5 years.

Note

Levels of Evidence [I–V] and Grades of Recommendation [A–D] as used by the American Society of Clinical Oncology are given in square brackets. Statements without grading were considered justified standard clinical practice by the experts and the ESMO faculty.
literature


5. Orsola A, Cecchini L, Raventos CX et al. Risk factors for positive findings in patients with high-grade T1 bladder cancer treated with transurethral resection of bladder tumour (TUR) and bacille Calmette-Guérin therapy and the decision for a repeat TUR. BJU Int 2009; 105: 202–207.


