clinical practice guidelines

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

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incidence

In 2008 in Europe an estimated 110 500 new cases of bladder cancer were diagnosed, leading to 38 200 cancer deaths. The age-standardized per 100 000 person years was 26.9 for males and 5.0 for females [1]. 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 World Health Organization (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 the latest WHO criteria and can concomitantly be graded according to the 1973 classification of high, low and intermediate grade carcinoma [2]. Ninety per cent of bladder carcinomas are transitional cell carcinomas.

staging and risk assessment

Most patients present with painless haematuria, though some present with dysuria and rarely symptoms of metastases. Most of the diagnosed cases of muscle-invasive bladder cancer (80–90%) present as primary invasive bladder cancer. Up to 15% of patients, however, have a history of non-muscle invasive bladder cancer (NMIBC), mainly high-risk cases.

Complete history and physical examination, blood counts, and creatinine and creatinine clearance tests should be undergone. Diagnosis of bladder cancer is based on cystoscopy and evaluation of the resected tissue. Cystoscopic examination and TUR with a bimanual examination under anaesthesia should be undergone following a standarized protocol. Complete resection of all tumour tissue should be intended/advocated when possible. Apart from biopsy and determination of number of tumours, the 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 ducts [III, C] [3]. Management of bladder cancer is based on the pathological findings of the biopsy, with attention to histology, grade and depth of invasion. Muscle-invasive bladder cancer (MIBC) should be staged according to the TNM system and grouped into categories (Table 2).

Local staging once histology confirms muscle invasion can be undergone with either computed tomography (CT) or magnetic resonance imaging (MRI). Both tests can be used to assess extravescial invasion but are unable to detect T3a disease (microscopic invasion of perivesical fat) and might be interfered with by a surgical (post-TUR) perivesical reaction. Similarly both tests are useful to detect enlarged nodes—over 8 mm in the pelvic area and over 1 cm for abdominal nodes—and distant metastasis. Hydronephrosis should also be taken into account as it has been shown to be an independent predictor of advanced bladder cancer stage and poor clinical outcome, and it predicts extravesical disease and node-positive disease [4]. A chest CT should be undergone at the same time as the abdomino-pelvis CT. Additional diagnostic tests, such as bone scan, should be performed if clinically indicated.

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Table 1. WHO/ISUP 1998 Consensus WHO, 2004

Papilloma
Papillary urothelial neoplasm of low malignant potential
Urothelial carcinoma low grade
Urothelial carcinoma high grade

WHO, World Health Organization; ISUP, International Society of Urologic Pathology.

Table 2.

Stage I	T1	N0	M0
Stage II	T2a–T2b	N0	M0
Stage III	T3a–T3b, T4a	N0	M0
Stage IV	T4b	N0	M0
	Any T	N1–N3	M0
	Any T	Any N	M1

treatment by disease stage

treatment of non-muscle-invasive bladder cancer

Complete TUR is the treatment of choice for any initial bladder tumour, followed by instillations according to risk stratification in NMIBC [5]. A second TUR is a reasonable option in high-risk NMIBC tumours either before intravesical therapy [II, B] or thereafter [III, B]. In the case of Tis or high-grade T1 failing bacille Calmette–Guerin (BCG), cystectomy should be considered due to the high risk of progression [III, B].

treatment of muscle-invasive bladder cancer

Radical cystectomy with extended lymphadenectomy is usually considered to be standard treatment for MIBC. Extended lymphadenectomy has been shown to be beneficial [III, A], and may be curative in patients with metastasis or micrometastasis to a few nodes. Progression-free survival and overall survival have been correlated with the number of lymph nodes removed during surgery. Reconstruction may be performed by either ileal conduit or bladder replacement depending on tumour characteristics and the patient's choice. Age is not a limiting factor for surgery any more, even though it has been shown that postoperative morbidity increases with age [6].

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

neoadjuvant and adjuvant therapy

Two large randomized trials and a meta-analysis support the use of neoadjuvant chemotherapy before cystectomy for T2 and T3 disease [7]. 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] [8]. However, based on retrospective studies showing some benefit of adjuvant chemotherapy in node-positive patients, this additional treatment may be considered in this context.

organ preservation therapy

The use of organ preservation therapy for MIBC is a reasonable alternative to cystectomy for patients seeking an alternative, and a palliative option for those who are medically unfit for surgery [III, B]. Contemporary protocols utilize aggressive endoscopic TUR alone, TUR plus radiotherapy, TUR plus chemotherapy, or—as the preferred treatment—a trimodality combination of TUR plus radiotherapy and chemotherapy. The initial prospective, randomized comparison of radiotherapy alone vs concomitant chemoradiotherapy in bladder cancer demonstrated an improved local control rate when cisplatin was given in conjunction with radiotherapy [II, A] [9]. There is now a second randomized controlled trial recently presented at ASCO and ASTRO—the BC2001 trial—that has shown improved results for radiochemotherapy [10]. In addition, the recently published BCON trial shows Carbogen improves results [11]. A cystoscopy with bladder biopsy is mandatory for response evaluation either midway through treatment or 2–3 months thereafter. If persistent or recurrent disease is observed at response evaluation or during follow-up (cystoscopy and urinary cytology every 3 months during the first 2 years, and every 6 months thereafter), prompt salvage cystectomy is recommended when possible [II, A].

Over the past 20 years, organ preservation by trimodality treatment has been investigated in prospective series from single centres and cooperative groups, with >1000 patients included [12]. Generally, ~20% of patients will present with residual tumour at restaging, and an additional 20–30% of patients with initial complete response will develop *de novo* or recurrent disease in the preserved bladder requiring additional treatment. Patients require the same regular follow-up as with radiotherapy (see previous paragraph), and up to 70% of the patients are free of tumour after the first cystoscopy control. However, during follow-up, a quarter of these individuals developed a new lesion requiring additional treatment. Five-year overall survival rates in the range of 50–60% have been reported, and about three-quarters of the surviving patients maintained their bladder [13, 14].

Clinical criteria helpful in determining ideal patients for bladder preservation include early tumour stage (including high-risk T1 disease [15], T2 <5 cm), a visibly complete TUR of bladder cancer (TURBT), absence of associated CIS and ureteral obstruction, and adequate bladder capacity and function [16]. Close coordination among all disciplines and the willingness of the patients to undergo lifelong surveillance are required to achieve optimal results.

treatment of advanced and metastatic disease

Cisplatin-containing combination chemotherapy with gemcitabine (GC) or MVAC (methotrexate, vinblastine, adriamycin and cisplatin) is standard in patients fit enough to tolerate cisplatin [I, A]. High-dose intensity MVAC with granulocyte colony-stimulating factor (G-CSF) is an option in fit

patients with limited advanced disease (less toxic and obtaining a higher response rate than standard MVAC) [17].Median survival in these patients is ∼14 months; long-term disease-free survival has been reported in ∼15% of patients, in 20.9% with lymph-node-only disease compared with only 6.8% with visceral metastases [18–20]. GC is less toxic than MVAC [I, A] [20]. MVAC is better tolerated with the use of G-CSF [21, 22] [III, B]. So far no improvement in survival was achieved with newer triplets, novel four drug regimens or dose-dense sequential chemotherapy [23–25]. The addition of a third agent (paclitaxel) to GC has been demonstrated to be of some benefit in a subset of patients having the bladder as the primary origin of the disease [I, B], and should be considered investigational [23]. Performance status (Karnofsky PS of ≤80%) and the presence of visceral metastases are independent poor prognostic factors for survival [26] (Figure 1).

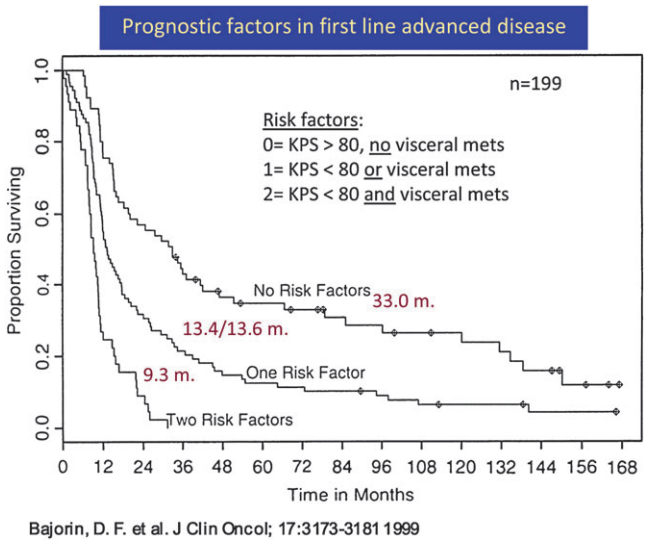

Figure 1. Prognostic factors in first-line advanced disease.

About 50% of patients are unfit for cisplatin-containing chemotherapy due to a poor PS, impaired renal function or co-morbidity. Patients unfit for cisplatin-based chemotherapy may be palliated with a carboplatin-based regimen or single-agent taxane or gemcitabine. Methotrexate/carboplatin/vinblastin (M-CAVI) and carboplatin/gemcitabine (CG) are active in patients unfit for cisplatin but without a statistically significant difference in overall survival and progression-free survival [I, A]. Severe acute toxicity was slightly higher on M-CAVI, which makes CG the preferred and reference treatment in unfit patients [27] [I, A]. Patients with PS 2 and impaired renal function and unfit patients in Bajorin prognostic group 2 have limited benefit from combination chemotherapy, and new strategies are needed [27] [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 [28]. The role of antiangiogenic therapy is investigational in first- and second-line therapy.

Palliative radiotherapy may be used to reduce symptoms such as pain or bleeding. Some data support that hypofractionated radiotherapy is as good as a fractionated course [29]. The role of consolidative radiation therapy after chemotherapy in patients with locoregional relapses is under evaluation [III, B].

treatment of relapse

Second-line phase II data are highly variable. Response rates with monochemotherapy are lower than with combinations, but progression-free survival has been short with both options. The results depend on patient selection. Recently, independent adverse prognostic factors for survival (PS >0, haemoglobin level <10 g/dl, and the presence of liver metastasis) for patients failing platinum-based chemotherapy have been defined and validated (Figure 2). They have to be considered for stratification in future trials and for assessing phase II data [30].

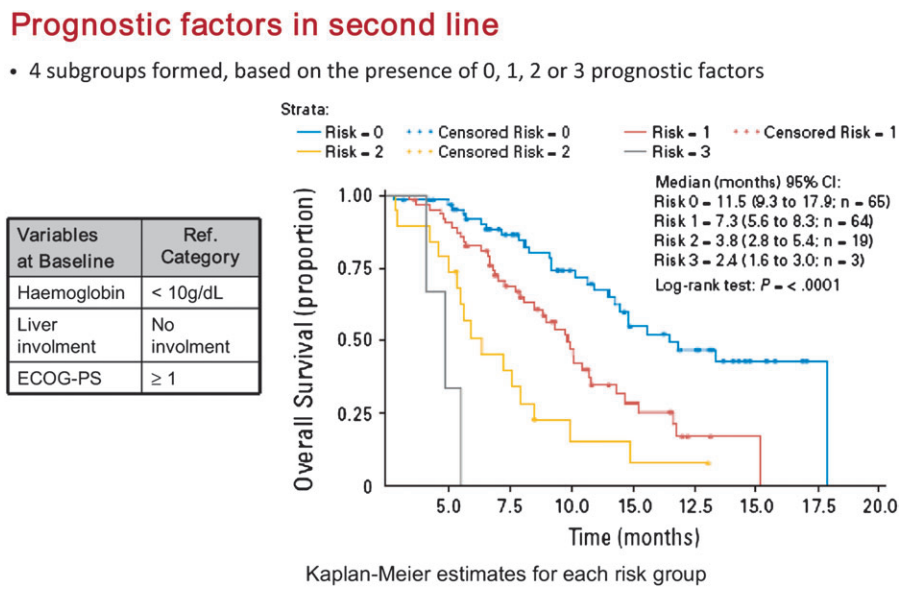

Figure 2. Prognostic factors in second-line advanced disease.

The only valid randomized phase III trial in patients progressing after first-line treatment with platinum-containing combination chemotherapy for metastatic disease tested vinflunine, a novel third-generation vinca alkaloid, plus best supportive care (BSC) vs BSC alone [31]. The results showed modest activity (overall response rate 8.6%), a clinical benefit with a favourable safety profile and a survival benefit in favour of vinflunine, which was statistically significant in the eligible patient population. This trial reached the highest level of evidence ever reported for second-line treatment. In Europe, vinflunine is the only approved drug in this setting [I, B]; however, it is unclear whether other agents used in this setting would have similar benefit.

response evaluation

Response evaluation with regular cystoscopy and cytology is mandatory 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 should be followed up every 3 months during the first 2 years, and every 6 months thereafter. After cystectomy, clinical control should take place every 3 months during the first 2 years and subsequently every 6 months for 5 years; this may be the case particularly in radically treated patients to detect salvageable recurrence

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.

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