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

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incidence and epidemiology

In Europe, an estimated 151 297 new cases of bladder cancer were diagnosed in 2012, with an age-standardised incidence rate (per 100 000 persons) of 17.7 for males and 3.5 for females. Overall, the annual crude incidence rate is 20.4/100 000. In 2012, there were 52 395 deaths from bladder cancer with an annual crude mortality rate of 7.1/100 000 [1]. Approximately 70% of patients with bladder cancer are >65 years of age.

The most common presenting symptom is painless haematuria, seen in >80% of patients. Others may also present with irritative symptoms such as dysuria, frequency or urgency. Symptoms of metastases such as bone or flank pain are rare. Most diagnosed cases of muscle-invasive bladder cancer (MIBC; 80%–90%) present as primary invasive bladder cancer. However, up to 15% of patients have a history of non-muscle-invasive bladder cancer (NMIBC), mainly high-risk cases.

pathological diagnosis

Pathological diagnosis should be made according to the World Health Organisation (WHO) classification (Table 1) from a biopsy obtained during transurethral resection of the bladder tumour (TURBT). Tumours should be graded as high and low grade according to the latest WHO criteria and can concomitantly be graded according to the 1973 classifications of high, low and intermediate grade carcinoma [3]. Ninety percent of bladder carcinomas are transitional cell carcinomas. The other types of urothelial cancer are relatively uncommon, including lymphoepithelioma-like or sarcomatoid carcinomas, micropapillary or nested variants and primary squamous cell carcinomas and adenocarcinomas [4]. This guideline relates to transitional cell carcinoma.

staging and risk assessment

A complete history and physical examination should be undertaken, together with laboratory tests evaluating full blood counts and renal function. Bladder ultrasonography most frequently gives an initial suspicious image, but final diagnosis of bladder cancer is based on cystoscopy and evaluation of the resected tissue. Cystoscopic examination and TURBT under anaesthesia should be carried out following a standardised protocol (Figure 1). Complete resection of all tumour tissue should be achieved when possible. At the time of TURBT, the number of tumours, their size(s) and the presence of extra-vesical extension or invasion of adjacent organs by bimanual examination 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 bladder muscle in the specimen, essential for 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 carried out to study a positive cytology, since the tumour could be located in the urothelium lining the prostatic urethra or the ducts [III, C] [6]. Management of bladder cancer is based on the pathological findings of the biopsy, with attention to histology, grade and depth of invasion. MIBC should be staged according to the tumour–node–metastasis (TNM) system and grouped into categories (Table 2).

Once histology confirms muscle invasion, local staging can be carried out with further imaging studies such as computed tomography (CT) or magnetic resonance imaging. Either test can be used to assess extra-vesical invasion but these tests are often unable to reliably differentiate T2 from T3a, T3b or even T4a.

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Importantly, because of interference by post-TURBT perivesical reactions, imaging is recommended before TURBT, if possible, when an invasive tumour is suspected (by ultrasound or cystoscopy). 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 stage bladder cancer and poor clinical outcome, and it predicts extra-vesical disease and node-positive disease [8]. A chest CT should be carried out at the same time as the abdomino-pelvis CT. Because a synchronous upper tract urothelial tumour may exist in 2.5% of patients, upper urinary tract imaging with either CT urograms, or i.v. or retrograde pyelograms should be undertaken to exclude this. In patients with high risk of metastases, additional tests may be undertaken, for example, bone scans and chest imaging.

Table 1. Pathologic Diagnosis of Urothelial Carcinoma of the Bladder (WHO/ISUP 1998 Consensus; WHO, 2004)

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

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

management of local/locoregional disease

treatment of non-muscle-invasive bladder cancer

Complete TURBT is the treatment of choice for any initial bladder tumour [9], followed by instillations according to risk stratification in NMIBC [I, A]. A second TURBT is a reasonable option in high-risk NMIBC tumours, either before intravesical therapy [II, B] or thereafter [III, B]. Presentations with very high-risk features, e.g. multiple grade 3 T1 tumours with TIS or increased depth of invasion, may be considered for cystectomy. In case of TIS or high-grade T1 failing Bacillus Calmette–Guérin (BCG), cystectomy should be considered due to the high risk of progression [III, B] (Figure 3).

treatment of muscle-invasive bladder cancer

Radical cystectomy (RC) with extended lymphadenectomy is usually considered to be the standard treatment of MIBC [10]. Extended lymphadenectomy has potentially been shown to be beneficial [III, A], and may be curative in patients with metastasis or micro-metastasis to a few nodes. Progression-free survival (PFS) and overall survival (OS) have been correlated with number of lymph nodes removed during surgery. Reconstruction may be carried out either by ileal conduit or bladder replacement, depending on tumour characteristics and patient choice. Age is no longer a limiting factor for surgery, even though postoperative morbidity increases with age [11].

External beam radiotherapy may be considered as a curative therapeutic option as part of a multimodality bladder-preserving approach [III]. When the patient is unfit for cystectomy,

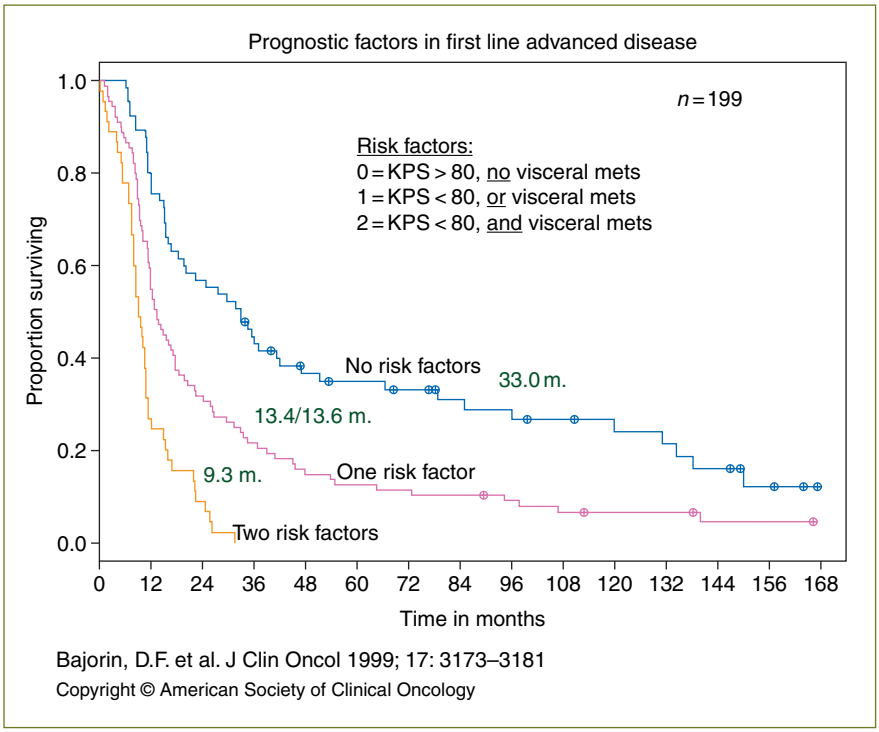

Figure 1. Prognostic factors in first-line advanced disease. Reprinted from [5] with permission of © 1999 American Society of Clinical Oncology. All rights reserved .

Table 2. TNM staging system for urothelial carcinoma of the bladder

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

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radiotherapy can also be offered for palliation (bleeding, pain). Curative external beam radiotherapy should be delivered with 3D conformal radiation therapy or intensity-modulated radiotherapy techniques, and ideally with image guidance.

neoadjuvant and adjuvant therapy

The use of cisplatin-based neoadjuvant chemotherapy for bladder cancer is supported by a meta-analysis of 11 randomised trials including 3005 patients. There was a 5% absolute increase in 5-year OS and a 9% absolute increase in 5-year disease-free survival (DFS) compared with RC alone [12]. This demonstrated survival benefit encourages the use of platinum-based combination chemotherapy before RC or definitive radiotherapy [I, A]. Alternatively, for adjuvant chemotherapy, an updated meta-analysis of nine randomised trials including 945 patients found an OS benefit [hazard ratio (HR) 0.77, 95% confidence interval (CI) 0.59–0.99, $P = 0.049$] and DFS benefit (HR 0.66, 95% CI 0.45–0.91, $P = 0.014$) among those who received cisplatin-based adjuvant chemotherapy. The DFS benefit was more apparent among those with positive lymph node involvement [13]. While there is still insufficient evidence for the routine use of adjuvant chemotherapy in clinical practice [I, A] [14], it is likely that high-risk patients, such as those with extravesical and/or node-positive disease that have not received neoadjuvant chemotherapy, will benefit most from adjuvant chemotherapy.

organ preservation therapy

The approach of organ preservation therapy for MIBC is a reasonable option for patients seeking an alternative to cystectomy and a palliative option for those who are medically unfit for surgery [III, B]. Contemporary protocols utilise aggressive endoscopic TURBT alone, TURBT plus radiotherapy, TURBT plus chemotherapy or—as the preferred treatment—a tri-modality combination of TURBT plus radiotherapy and chemotherapy. The initial prospective, randomised comparison of radiotherapy alone versus concomitant chemoradiotherapy in bladder cancer demonstrated an improved local control rate when cisplatin was given in conjunction with radiotherapy [II, A] [15]. A second trial showed that the addition of carbogen and nicotinamide (bladder carbogen nicotinamide) to radiotherapy significantly reduced the risk of relapse and death [16]. A third and recently published multicentre randomised trial (the BC2001 trial) has demonstrated improved results for chemoradiotherapy using the combination of 5-fluorouracil and mitomycin C in terms of locoregional control [17]. 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 more than 1000 patients included [18]. Generally, ~20% of patients will present with residual tumour at re-staging, and ≤70% of the patients are tumour free after the first cystoscopy control. 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). However, during follow-up, one-quarter of these individuals developed a new lesion requiring additional treatment. Five-year OS rates in the range of 50%–60% have been reported, and about three-quarters of the surviving patients retained their bladder [19, 20].

Clinical criteria helpful in determining whether patients are ideal for bladder preservation include early tumour stage (including high-risk T1 disease [21], T2 <5 cm), a visibly complete TURBT, absence of associated CIS and ureteral obstruction and adequate bladder capacity and function [22]. Close coordination among all disciplines and the willingness of the patients to undergo lifelong surveillance are required to achieve optimal results.

management of advanced and metastatic disease

Cisplatin-containing combination chemotherapy with GC (gemcitabine/cisplatin), or MVAC (methotrexate, vinblastine, adriamycin and cisplatin) is standard in advanced surgically unresectable and metastatic patients fit enough to tolerate cisplatin [I, A]. Median survival in these patients is about 14 months; long-term DFS has been reported in about 15% of patients; in 20.9% with lymph-node-only disease compared with only 6.8% with visceral metastases [23–25]. So far, no improvement in survival has been achieved with newer triplets, novel four-drug regimens or dose-dense chemotherapy [26–28]. GC is less toxic than MVAC [I, A] [25]. MVAC is better tolerated with the use of granulocyte colony-stimulating factor (G-CSF) [29, 30] [III, B]. High-dose intensity MVAC with G-CSF, delivered in half the time of traditional MVAC, is an option for fit patients with limited advanced disease, given its lower toxicity profile and superior response rate compared with standard MVAC [31]. The addition of a third agent (paclitaxel) to GC has been shown 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 as an option in highly selected patients [28]. Performance status (PS)

(Karnofsky PS of 80% or less) and the presence of visceral metastases are independent poor prognostic factors for survival [5] (Figure 1).

About 50% of patients are unfit for cisplatin-containing chemotherapy due to a poor PS, impaired renal function or comorbidity. Patients unfit for cisplatin-based chemotherapy may be palliated with a carboplatin-based regimen or single-agent taxane or gemcitabine. Methotrexate/carboplatin/vinblastine (M-CAVI) and carboplatin/gemcitabine (CarboGem) are active in patients unfit for cisplatin, but without a statistically significant difference in OS and PFS [I, A]. Severe acute toxicity was slightly higher on M-CAVI, which makes CarboGem the preferred and reference treatment in unfit patients [I, A] [32]. 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 [II, A] [32].

Selected patients with locally advanced disease (T4b N1) may be candidates for cystectomy and lymph node dissection or definitive radiotherapy following systemic therapy [33]. The role of anti-angiogenic therapy is investigational in first- and second-line therapy.

Palliative radiotherapy may be used to reduce symptoms such as pain or bleeding. 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 with results depending on patient selection. Response rates for treatment of relapse with mono-chemotherapy are lower than with combinations, but PFS has been short with both options. 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). These factors should therefore be considered for stratification in future trials and for assessing phase II data [34].

The only valid randomised 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) versus BSC alone [35]. 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 unknown whether other agents used in this setting would have a similar benefit.

personalised medicine

Overall, personalised cancer therapies hold the promise to improve clinical outcomes, using readily obtainable biomarkers of response to predict their clinical benefits.

Advanced technologies such as high-throughput transcript profiling, microarrays, metabolomics and proteomics have provided us with tools to enhance our understanding of the molecular pathways underlying bladder cancer. Intense research efforts in this area have led to the discovery of numerous molecular markers that may be useful for screening, early diagnosis and surveillance as well as staging and prognosis [36]. Current

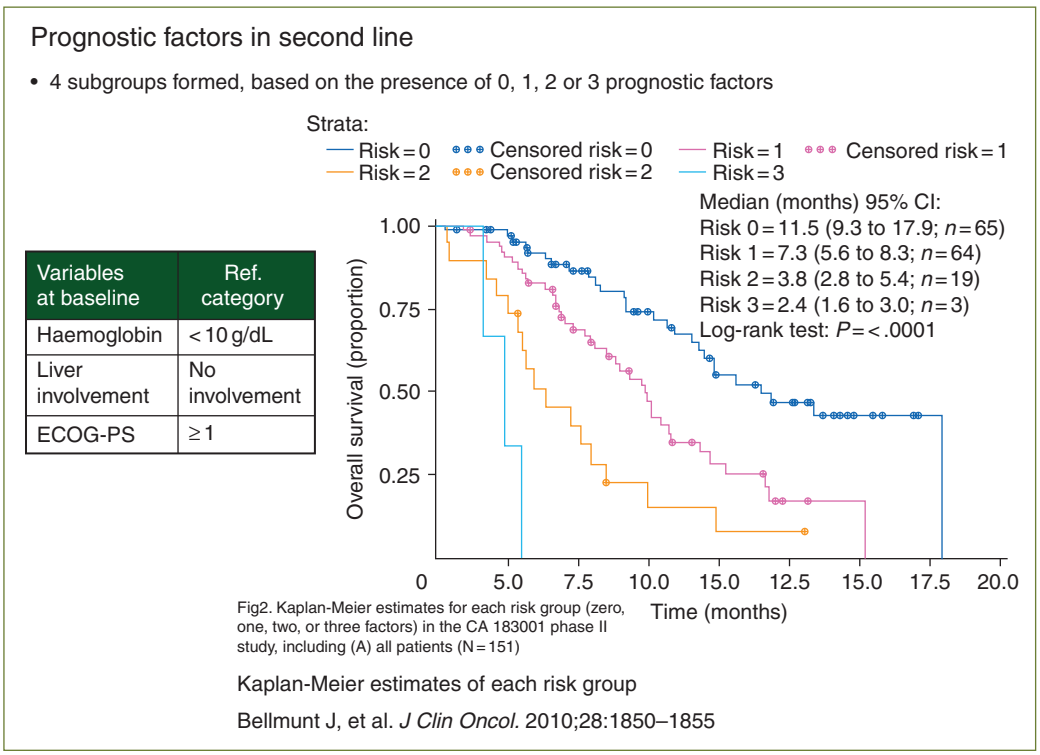

Figure 2. Prognostic factors in second line. Reprinted from [34] with permission of © 2010 American Society of Clinical Oncology. All rights reserved.

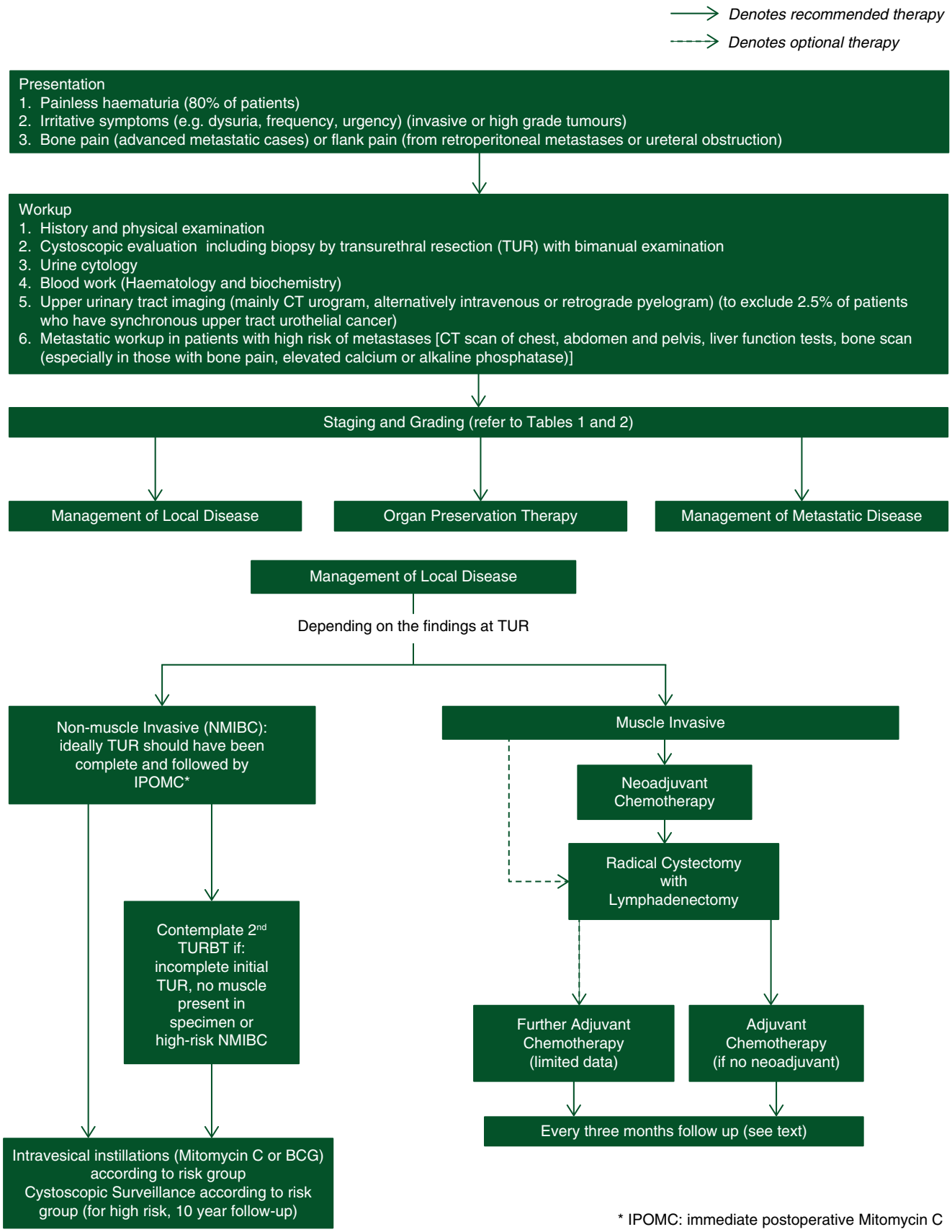

Figure 3. Overview of clinical management of patient with suspected bladder cancer (local disease, organ preservation therapy, and metastatic disease).

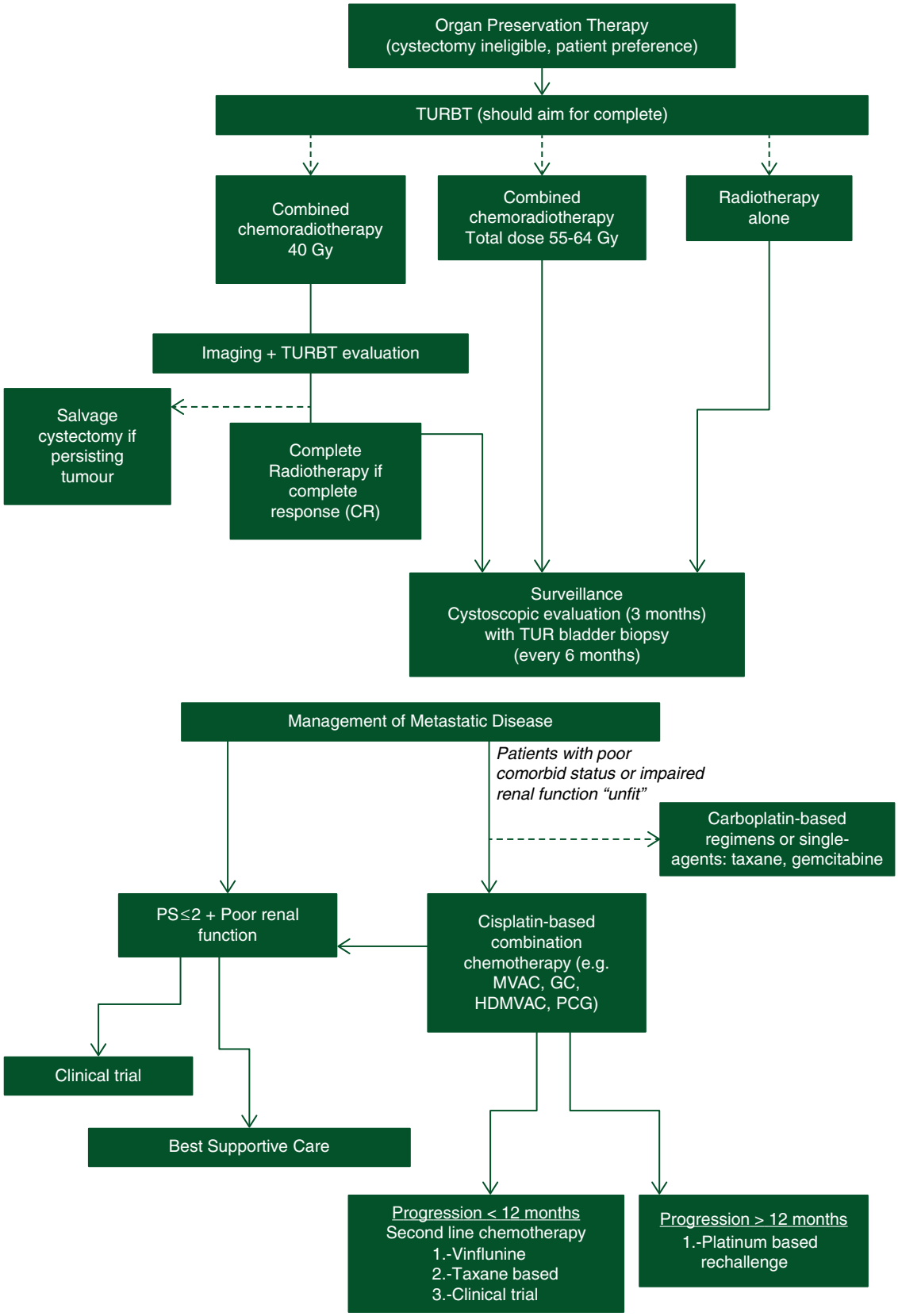

Fig. 3 *Continued*

Table 3. Levels of evidence and grades of recommendation (adapted from the Infectious Diseases Society of America-United States Public Health Service Grading System[a])

Levels of evidence	
I	Evidence from at least one large randomised, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomised trials without heterogeneity
II	Small randomised trials or large randomised trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case–control studies
V	Studies without control group, case reports, experts opinions
Grades of recommendation	
A	Strong evidence for efficacy with a substantial clinical benefit, strongly recommended
B	Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, …), optional
D	Moderate evidence against efficacy or for adverse outcome, generally not recommended
E	Strong evidence against efficacy or for adverse outcome, never recommended

[a]By permission of the Infectious Diseases Society of America [47].

evidence suggests that screening for bladder cancer on a population level is not helpful for improving survival [V, C].

For NMIBC, cystoscopy alone remains the most cost-effective method to detect bladder cancer recurrence [II or III, B], despite the fact that it is an invasive and relatively expensive procedure. As for voided urine cytology, it is highly specific but not sensitive enough, especially for low-grade tumours. Improvement in scoring systems, such as the European Organisation for Research and Treatment of Cancer (EORTC) scoring system, or the Spanish Urological Club for Oncological Treatment (CUETO) scoring system, for the broad spectrum of NMIBC, as well as deeper knowledge on the impact of depth of invasion and associated CIS in high-grade T1 (HGT1) bladder cancer, should aid in a better risk stratification of NMIBC [37–39]. Presently, there are five bladder tumour marker tests, namely BTA-Stat, BTA-TRAK, NMP-22, uCyt+ and UroVysion that may be used for diagnosis and/or follow-up [36], but none has been shown to be superior to urine cytology and cystoscopy.

Molecular analyses have identified genetic and epigenetic alteration in high-grade urothelial carcinomas, including ≤60% of genomic alterations that could be treated by drugs that are already available or are in clinical testing [40]. Some potential new targets for treatment intervention have been described for urothelial tumours. Mutations in the receptor tyrosine kinases (*RTK*)-*RAS*-*RAF*, phosphoinositide 3-kinase (*PI3K*)/*AKT*/mammalian target of rapamycin (mTOR) pathways and regulators of G1-S cell cycle progression such as TP53 and RB1 have been the most consistently reported [40].

In addition, a large proportion of urothelial tumours also harbour mutation and/or gene amplification that are potentially therapeutic targets, and these include *FGFR3* mutations, *PTEN* deletions and FGFR1, CCND1 and MDM2 amplifications [41]. Moreover, aberrations of the chromatin remodelling genes (*UTX*, *MLL-MLL3*, *CREBBP-EP300*, *NCOR1*, *ARID1A* and *CHD6*) and, more recently, *STAG2* mutations have also been documented in more than half of urothelial carcinomas, including low- and high-grade tumours [40, 42–44]. However, the functional effect of mutations in these genes encoding epigenomic regulatory proteins remains relatively unknown. The identification of these driving genomic alterations, even if occurring in only a small subset of bladder cancer patients, may lead to the development of patient-specific therapies. This has been the case of the recently described mutations in *TSC1* predicting response to mTOR inhibitors like everolimus [40, 45], or in the *PIK3CA* gene, mutated in up to 26% of cases [46] that may predict sensitivity to *PIK3CA*/mTOR inhibitors.

follow-up and long-term implications

There is no generally accepted follow-up protocol; therefore, the possible options could be as follows: in NMIBC, regular cystoscopy and cytology is mandatory every 3–6 months based on the high or low risk during the first 2 years, and every 6–12 months thereafter to assess tumour response, progression or recurrence.

After definitive treatment of MIBC with RC, urine cytology, liver function and renal function tests should be carried out every 3–6 months for 2 years, and subsequently as clinically indicated. Imaging of the chest, upper tract, abdomen and pelvis every 3–6 months for 2 years should also be undertaken based on the risk of recurrence, and subsequently as clinically indicated. Additionally, urethral wash cytology may be carried out every 6–12 months if urethrectomy has not been carried out or if there is prior history of CIS.

For MIBC patients in whom a bladder preservation strategy has been adopted, there is a need to evaluate response to treatment after induction chemoradiation. After completion, the same follow-up regimen as for RC is recommended; however, cystoscopy and urine cytology plus random biopsies every 3–6 months for 2 years are necessary. During follow-up, monitoring of long-term treatment toxicities and potential recurrences of secondary tumours should be carried out.

For those who undergo systemic chemotherapy, response evaluation every two to three cycles using the initial radiographic tests carried out during the work-up is also necessary. Providing optimal care for patients will also involve addressing psychosocial implications of all above-mentioned treatment strategies.

note

Levels of evidence and grades of recommendation have been applied using the system shown in Table 3. Statements without grading were considered justified standard clinical practice by the experts and the ESMO faculty.

conflict of interest

JB has reported Advisory board for and lecture fees from Pierre Fabre. MdS has reported study grants from Pierre Fabre Oncology; she also reported Honoraria and Consultancy fees from Amgen, Astellas, Bayer, Celgene, Dendreon, Ferring, GlaxoSmithKline, Janssen Cilag, Novartis, Pfizer, Pierre Fabre, Roche, Sanofi, Shionogi, Takeda and Teva/Oncogenex. AO, JL, TW and AH have reported no potential conflicts of interest.

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