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Guidelines

Treatment of Muscle-invasive and Metastatic Bladder Cancer: Update of the EAU Guidelines

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Abstract

Context: New data regarding treatment of muscle-invasive and metastatic bladder cancer (MiM-BC) has emerged and led to an update of the European Association of Urology (EAU) guidelines for MiM-BC.
Objective: To review the new EAU guidelines for MiM-BC with a specific focus on treatment.
Evidence acquisition: New literature published since the last update of the EAU guidelines in 2008 was obtained from Medline, the Cochrane Database of Systematic Reviews, and reference lists in publications and review articles and comprehensively screened by a group of urologists, oncologists, and a radiologist appointed by the EAU Guidelines Office. Previous recommendations based on the older literature on this subject were also taken into account. Levels of evidence (LEs) and grades of recommendations (GRs) were added based on a system modified from the Oxford Centre for Evidence-based Medicine Levels of Evidence.
Evidence synthesis: Current data demonstrate that neoadjuvant chemotherapy in conjunction with radical cystectomy (RC) is recommended in certain constellations of MiM-BC. RC remains the basic treatment of choice in localised invasive disease for both sexes. An attempt has been made to define the extent of surgery under standard conditions in both sexes. An orthotopic bladder substitute should be offered to both male and female patients lacking any contraindications, such as no tumour at the level of urethral dissection. In contrast to neoadjuvant chemotherapy, current advice recommends the use of adjuvant chemotherapy only within clinical trials. Multimodality bladder-preserving treatment in localised disease is currently regarded only as an alternative in selected, well-informed, and compliant patients for whom cystectomy is not considered for medical or personal reasons. In metastatic disease, the first-line treatment for patients fit enough to sustain cisplatin remains cisplatin-containing combination chemotherapy. With the advent of vinflunine, second-line chemotherapy has become available.
Conclusions: In the treatment of localised invasive bladder cancer (BCa), the standard treatment remains radical surgical removal of the bladder within standard limits, including as-yet-unspecified regional lymph nodes. However, the addition of neoadjuvant chemotherapy must be considered for certain specific patient groups. A new drug for second-line chemotherapy (vinflunine) in metastatic disease has been approved and is recommended.

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1. Introduction

This is the first major update of the guidelines on muscle-invasive and metastatic bladder cancer (MiM-BC) published by the European Association of Urology (EAU) Guideline Panel in 2008. Most of the change has taken place in the surgical and medical treatment of the disease, and this overview therefore focuses on altered recommendations for the management of MiM-BC.

The intention of these EAU guidelines, produced by a panel of international multidisciplinary experts in this field, is to support urologists in assessing evidence-based management of MiM-BC and incorporating guideline recommendations into their clinical practice. Comprehensive literature searches were designed for each section of the MiM-BC guideline with the help of an expert external consultant. Following detailed internal discussion, searches were carried out in the Cochrane Database of Systematic Reviews, the Cochrane Collaboration's Central Register of Controlled Clinical Trials, Medline, and Embase on the Dialog DataStar platform. The searches used the narrowest single terms available in the controlled vocabulary of the respective databases. Those terms were *urinary bladder neoplasm* in Medical Subject Headings (MeSH) for Medline and *bladder cancer* in Emtree for Embase.

Results of all searches were scan-read by panel members. In many cases, there was a high "numbers needed to read" because of the sensitivity of the search. There is clearly a need for continuous reevaluation of the information presented in the current guideline by an expert panel. Even though the current guideline update contains information on the treatment of an individual patient according to a standardised approach, it must be emphasised that the recommendations based on the literature research cannot be binding because of either a nonstandardised approach or an unusual situation or desire in individual patients.

In this article, we have grouped the various discussions and recommendations of treatment options of MiM-BC into localised bladder cancer (BCa) and metastatic BCa. The level of evidence (LE) and grade of recommendation (GR) provided in this guideline of treatment options follow the listings outlined in the full-text version (see http://www.uroweb.org/guidelines/online-guidelines/) [1].

2. Localised invasive bladder cancer

Localised invasive BCa is defined as histologically verified T≥1 N0 M0 disease.

2.1. Neoadjuvant chemotherapy

Neoadjuvant chemotherapy is administered to patients with clinically operable, muscle-invasive (N0 M0), urothelial cancer (UC) of the urinary bladder before the planned definitive surgery (or radiation). Neoadjuvant chemotherapy has many advantages: (1) It is delivered at the earliest time-point, when the burden of micrometastatic disease is expected to be low; (2) there is a potential reflection of in-vivo chemosensitivity; (3) the tolerability of chemotherapy is expected to be better before cystectomy rather than after it; and (4) hypothetically, patients with micrometastatic disease might respond to neoadjuvant therapy and reveal favourable pathologic status, as determined mainly by negative lymph node status and negative surgical margins.

However, neoadjuvant chemotherapy also has potential disadvantages: (1) Patients without micrometastatic disease—approximately half of which are clinically N0 M0 patients—will receive unnecessary treatment; (2) staging errors may hypothetically lead to overtreatment; (3) the delay in cystectomy may compromise outcomes in patients who do not respond to chemotherapy [2–4]; and (4) chemotherapy may have side-effects that affect the outcome of surgery and type of urinary diversion (UD) [5].

In a randomised trial of cystectomy following neoadjuvant chemotherapy, the overall morbidity showed the same distribution of postoperative grade 3–4 complications in both trial arms. However, preoperative anaemia and neuropathy were more common in the chemotherapy-treated group [5]. In the combined Nordic trials NCS1+NCS2 (n = 620), neoadjuvant chemotherapy did not have any major adverse effect on the percentage of performable cystectomies [6].

As a result of a 5–8% overall survival (OS) advantage in recently published studies and meta-analyses, neoadjuvant cisplatin-containing combination chemotherapy should be considered and discussed with the patient in cases of muscle-invasive, node-negative, and nonmetastatic (N0 M0) urinary bladder carcinoma, irrespective of definitive treatment [6,7] (LE: 1).

In patients, a performance status (PS) ≥2 and/or impaired renal function are contraindications for neoadjuvant chemotherapy (LE: 1). Generally, chemotherapy alone is not recommended as the primary therapy for localised, muscle-invasive, N0 M0, UC of the bladder [8] (LE: 1). A summary of the treatment recommendations can be found in Table 1.

2.2. Preoperative radiation therapy

Several retrospective studies have looked at the effect of preoperative radiation therapy (RT) in patients with BCa, suggesting downstaging in 40–65% of patients, improved local control in 10–42% of patients, and improved survival in 11–12% of patients. Improved local control seemed highest

Table 1 – Recommendations for neoadjuvant chemotherapy

Recommendations	GR
Neoadjuvant cisplatin-containing combination chemotherapy should be offered in muscle-invasive BCa, irrespective of further treatment.	A
Neoadjuvant chemotherapy is not recommended in patients with a PS ≥2 and/or impaired renal function.	B
For localised, muscle-invasive, N0 M0 UC of the bladder, chemotherapy alone is not recommended as the primary therapy.	A

GR = grade of recommendation; BCa = bladder cancer; PS = performance status; UC = urothelial carcinoma.

in T3b tumours, and a pathologically confirmed, complete remission after RT appeared to be a positive prognostic factor for survival.

Randomised studies have investigated preoperative RT [9]. Although the results from these trials suggested there was an advantage in both downstaging and survival—especially in ≥pT3 tumours—as well as better results in pathologic complete responders and limited toxicity of neoadjuvant RT, all the studies had severe limitations, including no documentation of the effect on local recurrences in all the studies. Furthermore, a meta-analysis of the trials showed an odds ratio (OR) for the difference in 5-yr survival of 0.71 (95% confidence interval [CI], 0.48–1.06). However, the meta-analysis was potentially biased by results from the largest trial, in which patients were not given the planned treatment. When the results of the largest trial were excluded, the OR became 0.95 (95% CI, 0.57–1.55), indicating that improved survival with preoperative RT had not been proven [9].

Although a more recent study has reached similar conclusions, the results, unfortunately, suffer from the same limitations [10]. Table 2 presents a summary of the conclusions and a recommendation regarding preoperative therapy.

2.3. *Cystectomy and urinary diversion*

To date, there have been no randomised studies comparing removal of the entire urinary bladder and associated lymph nodes with bladder-preserving treatment strategies. However, efforts to evaluate multimodality treatment in a prospective, randomised fashion are being developed [11]. Radical cystectomy (RC) remains the preferred treatment option for patients with advanced, localised urothelial BCa [12] (LE: 2a).

2.3.1. *Standard surgical technique*

In male patients, the literature over the past two decades has set the standard of surgical limits for curative RC, which involves complete removal of the bladder with all macroscopically visible and resectable bladder-perforating tumour extensions, removal of the adjacent distal ureters, and removal of the lymph nodes corresponding to the tumour-bearing bladder. Technical variations from this standard that may improve patients' quality of life (QoL) include preservation of (1) anterior and membranous urethra, including the rhabdosphincter, to enable an orthotopic neobladder; (2) parts of the prostate and seminal vesicles for reasons of fertility, potency, and continence; and (3) intrapelvic autonomic and sensory nerves to enhance potency and continence. However, these variations must be carefully judged against the potential for increased oncologic risk [13] (LE: 3).

Preservation of parts of the prostatic gland during resection carry risks as high as 23–54% of unsuspected adenocarcinomas, of which up to 29% may be clinically significant, leading to local recurrence or even metastasis [14–16]. Because UC may be present in the prostate, in some series, only 26–33% of patients undergoing cystoprostatectomy were found to have neither prostate cancer nor prostatic UC [17]. A recently developed technical variation aimed at better preserving the surrounding autonomic nerves is deliberately to leave the seminal vesicles, with or without the prostatic capsule. The results for potency versus oncologic risk in small series of selected patients have been encouraging, but long-term confirmation is needed using larger series [18,19].

In female patients, standard anterior pelvic exenteration includes the bladder, entire urethra, adjacent vagina, uterus, distal ureters, and respective lymph nodes (LE: 3; GR: C). Unless the primary tumour is located at the bladder neck or in the urethra, it is possible to preserve a major part of the functioning female urethra and (provided a complete tumour resection is possible) its supplying autonomous nerves in case of a planned orthotopic neobladder [13,20] (LE: 3). New data also question the necessity of removing the uterus or any portion of the vagina in favour of providing improved anatomic support for the neobladder and better preservation of surrounding autonomous nerves.

In both sexes, the length of the distal ureteral segment to be removed with the bladder has not been specified. It depends on oncologic status (eg, tumour extension or the presence of carcinoma in situ and the type of subsequent UD). In a recent study, a frozen section of the distal ureteral margins had a sensitivity of 74% and a specificity of 99.8%, resulting in an overall accuracy of 98.3% [21]. With a serial sectioning strategy, most initially positive ureteral margins can be converted into negative final margins. These patients are at decreased risk of developing upper urinary tract recurrent disease [22,23].

Current literature unanimously supports the simultaneous removal of pelvic lymph nodes together with the tumour-bearing bladder (LE: 3). Retrospective studies have shown that extended lymphadenectomy can improve survival in patients with muscle-invasive BCa. The true curative value of lymph node dissection (LND), however, is still unknown, and a standardised LND has yet to be defined [7,24].

Several localisation studies with regards to lymphadenectomy [24–27] have demonstrated both retrospectively and prospectively that lymph nodes in BCa patients are not found outside the pelvis if the pelvic lymph nodes are free of tumour [28] (LE: 3). Furthermore, both progression-free survival and OS may be correlated with the amount of lymph nodes removed during surgery [24,25].

Table 2 – Preoperative radiotherapy: conclusions and recommendations

Conclusions:	LE
Preoperative RT can lead to downstaging.	2
Toxicity is not significantly increased.	3
Recommendation:	GR
Preoperative RT for operable muscle-invasive BCa followed by RC does not increase survival and therefore is not recommended.	B

LE = level of evidence; RT = radiation therapy; GR = grade of recommendation; BCa = bladder cancer; RC = radical cystectomy.

Table 3 – Conclusions and recommendations for radical cystectomy and urinary diversion

Conclusions:	LE
Male patients: Standard curative RC is defined as the complete removal of the urinary bladder and all visible tumour, adjacent distal ureters, and lymph nodes corresponding to the tumour-bearing bladder.	3
Male patients: Preservation of the entire or anterior urethra, rhabdosphincter, prostate, seminal vesicles, and intrapelvic autonomic and sensory nerves are all technical variations to the above standard.	3
Female patients: Standard anterior pelvic exenteration includes removal of the entire urethra, adjacent vagina, uterus, distal ureters, and respective lymph nodes.	3
Ureterocutaneostomy is the least burdensome type of UD for patients with compromised general health.	3
Recommendations:	GR
In T2–T4a N0 M0 and high-risk non–muscle-invasive BCa, RC remains the recommended treatment.	A*
In female patients, tumour permitting, preserve a major part of a functioning urethra and its supplying autonomous nerves in the case of a planned orthotopic neobladder.	C
Simultaneous removal of pelvic lymph nodes is recommended as an integral part of RC and anterior pelvic exenteration.	B
Laparoscopic cystectomy and pelvic lymphadenectomy, with or without robotic assistance, in conjunction with extracorporeal UD is an option for surgical treatment.	C
Treatment is recommended at centres experienced in cystectomy, major types of diversion techniques, and postoperative care [45,49].	C
In the absence of any interfering psychological or physical abnormality or disease, an orthotopic bladder substitute should be offered to male and female patients lacking any oncologic contraindications.	C

LE = level of evidence; RC = radical cystectomy; UD = urinary diversion; GR = grade of recommendation; BCa = bladder cancer.
* Upgraded following panel consensus.

Both laparoscopic RC and the robot-assisted procedure have been shown to be feasible [29]. However, the recommendation for minimally invasive techniques is still optional and reserved for surgeons skilled in this technique for reasons of selection bias, including the patient's general health status, tumour stage, or type of UD chosen as well as the generally much smaller, reported series compared to open cystectomy reports [30].

Laparoscopic intracorporeal construction of UD with or without robotic assistance has been tested in small series only [29,31]. It is a challenging and lengthy procedure with the technical equipment currently available and must therefore be regarded as experimental. Laparoscopic cystectomy and pelvic lymphadenectomy (with or without robotic assistance), with extracorporeal construction of UD, is an option for surgical treatment (LE: 3).

2.3.2. *Urinary diversion after radical cystectomy*

From an anatomic standpoint, three alternative forms of UD outlet are presently used after cystectomy: abdominal, urethral, and rectosigmoid. In the case of an abdominal or rectosigmoid diversion, the ureters can be diverted either directly (ureterocutaneostomy or ureterorectosigmoidostomy) or by interposing an intestinal segment, such as stomach, ileum, colon, or appendix [32]. According to large series, the most common abdominal rerouting is ureteroileocutaneostomy or a Bricker ileal conduit [12].

In a recent retrospective comparison with short or median follow-up of 16 months, the diversion-related complication rate was considerably lower for ureterocutaneostomy compared to an ileal or colon conduit [33]. Despite the limited comparative data available, it has to be taken into consideration that older data and clinical experience suggest stricturing at the skin level and ascending urinary tract infection more frequently as compared to ileal conduit. In a retrospective study comparing various forms of intestinal diversion, ileal conduits had fewer late complications than continent abdominal pouches or orthotopic neobladders [34].

Several studies have compared certain aspects of health-related QoL, including sexual function, urinary continence, and body image, in patient cohorts with different types of UD. However, more research is necessary in this field. It is not possible to evaluate QoL issues for a type of UD without taking into account other factors, such as preoperative tumour stage, patient age and expectations, functional situation, socioeconomic status, experience of the treating urologist, and possible surgical complications. Currently, it is not possible to recommend a particular type of UD, except to say that ureterocutaneostomy is surgically the least-burdensome type of diversion for the patient (LE: 3).

Patients undergoing any type of UD have to be motivated to learn to cope with their diversion and to develop the manual dexterity required. Debilitating neurologic and psychiatric illnesses, limited life expectancy, impaired liver or renal function, and UC of the urethral margin or other surgical margins have been defined as contraindications to more complex forms of intestinal UD (LE: 2b). Relative contraindications specific to an orthotopic neobladder are high-dose preoperative RT, complex urethral stricture disease, and severe urethral sphincter-related incontinence [35–38] (LE: 2b).

There are no explicit data that age precludes any type of UD. However, because of an increasing number of underlying morbidities and reduced general health status, most patients older than 75 yr of age receive an incontinent form of UD following cystectomy [39].

Standard RC in male patients with bladder neoplasms includes removal of the entire bladder, prostate, seminal vesicles, distal ureters (length of the segment undefined), and corresponding lymph nodes (extent undefined; LE: 2b). Currently, it is not possible to recommend a particular type of UD. However, most institutions prefer ileal orthotopic neobladders and ileal conduits based on clinical experience [12,36]. In selected patients, ureterocutaneostomy is surgically the least-burdensome type of diversion (LE: 3; GR: C). Recommendations related to RC and UD are listed in Table 3.

Table 4 – Largest single-institution studies looking at recurrence-free survival rates after cystectomy [38,43,44]

Reference	No. of patients		Median follow-up, mo	RFS	Recurrence	
	Male	Female	5 yr, %	10 yr, %	Local only, %	Distant only, %
Stein [43]	1054	122	68	66	7	22
Madersbacher [44]	507	45	62	50	8	35
Hautmann [38]	788	53	65	59	9	18

RFS = recurrence-free survival.

Table 5 – Recommendations regarding outcome after surgery

Recommendation:	GR
Oncologic outcome:	
For patients with inoperable locally advanced tumours (T4b), primary RC is a palliative option and not recommended as a curative treatment.	C
In patients with invasive BCa >80 yr of age, cystectomy is an option.	C
For palliative cystectomy, surgery-related morbidity and QoL should be weighed against other options.	C
Surgical outcome:	
Surgical complications of cystectomy and UD should be reported in a uniform grading system. Currently, the best-adapted graded system for cystectomy is the Clavien grading system.	B
Comorbidity, age, previous treatment for BCa or other pelvic diseases, surgeon and hospital volume of cystectomy, and type of UD influence surgical outcome.	B

GR = grade of recommendation; RC = radical cystectomy; BCa = bladder cancer; QoL = quality of life; UD = urinary diversion.

2.3.3. *Oncologic outcome after surgery*

Recurrence-free survival (RFS) and OS in male and female patients is reported as 66–68% and 58–66% at 5 yr and 60–73% and 43–49% at 10 yr, respectively [8]. In node-positive patients, 10-yr disease-specific survival and OS rates were reduced to 27.7% and 20.9%, respectively [40]. These results (Table 4) have to date not been reached in stage-equivalent large studies with bladder-sparing treatment alternatives.

Nomograms on cancer-specific survival (CSS) following RC have been developed and externally validated, but their wider use cannot be recommended prior to further data [41,42]. In a retrospective series of 768 male patients by Stein et al [37], the overall urethral recurrence rate was 6%, irrespective of UD. In a multivariate statistical analysis, prostatic involvement by the primary tumour and cutaneous UD was independently associated with an increased risk for the development of second primary tumours (LE: 2b). The calculated risk of second primary tumours was 5% and 9% for patients with an orthotopic and cutaneous UD, respectively. A difference for second primary tumours, depending on initial prostatic tumour involvement, was apparent for both superficial (12% vs 5%) and invasive UC (18% vs 5%).

Cystectomy is associated with the greatest risk reduction in disease-related and non–disease-related death in patients older than 80 yr of age [45]. The largest, retrospective, single-institution study on cystectomy to date demonstrated that patients older than 80 yr of age did have an increased postoperative morbidity but not increased mortality [45] (LE: 3).

Remnant disease may be inevitable in patients with locally advanced pelvic cancer and urinary bladder involvement. However, in these cases, palliative RC and UD—with or without using intestinal segments—is performed only for the relief of symptoms such as pain, recurrent bleeding, urgency, and fistula formation. The morbidity associated with surgery and QoL should be weighed against other options (LE: 3) [45–47]. Table 5 lists the recommendations regarding oncologic outcome after surgery.

2.3.4. *Outcome of radical surgery*

Most surgical complications are associated with UD, of which a great portion is related to the use of intestinal segments [35,38]. Variables such as patient factors, surgeon's skills, hospital volume, and type of UD all influence the rate, type, and severity of surgical complications (Table 5) [45,48,49].

When reporting surgical complications in cystectomy, regardless of the technique used, a standardised and reproducible classification of surgical complications should be applied. Complications of several urologic procedures, including open [50] and laparoscopic cystectomy [51], have recently been reported using the modified, five-grade Clavien system, which has been tested in >6300 surgical procedures [52]. Alternatively, complications have been reported with the Common Terminology Criteria for Adverse Events [53]. Early and late complications following surgery are defined as those that occur within 90 d and after 90 d, respectively [50,54]. In the most recent reports on cystectomy, an adverse event of any grade was seen in 54–58% of patients [50,53,55].

2.4. *Bladder-sparing treatments for localised disease*

2.4.1. *Definitive external-beam radiation therapy*

The target field usually comprises the bladder only, with a safety margin of 1.5–2 cm. The target dose for curative RT for BCa is 60–66 Gy. Modern RT techniques result in major, late gastrointestinal or genitourinary morbidity in < 5% of patients. Overall 5-yr survival rates range between 30% and 60%, with a CSS rate of 20–50% [56–58]. Prognostic factors for RT were addressed in a recent Italian single-institution

Table 6 – Bladder-sparing treatments for localised disease

Definitive EBRT	
Conclusion:	LE
Previously irradiated patients undergoing RC later on have a higher risk of early complications.	3
Recommendations:	GR
Definitive EBRT:	
EBRT as a primary approach is only recommended when the patient is unfit for cystectomy.	C
Chemotherapy:	
Chemotherapy alone is not recommended as the primary therapy for localised BCa.	A

EBRT = external-beam radiation therapy; RC = radical cystectomy; GR = grade of recommendation; BCa = bladder cancer.

series of 459 irradiated patients, including approximately 30% of unfit T1 patients, with an average of 4.4-yr follow-up. Significant factors were age, T category (for all end points), and tumour dose (only for failure-free survival) in a multivariate survival analysis [59]. Based on available trials, a Cochrane analysis has demonstrated that RC has an OS benefit compared with RT [60]. However, external-beam RT (EBRT) can be an alternative in patients unfit for radical surgery, with a cystoscopically assessed, complete remission rate at 3 mo of 78% and a 3-yr local control rate of 56% [61] (Table 6). A recent single-institution report investigating the 90-d early complication rate of RC after full-dose RT found a higher complication rate according to the Clavien reporting system in 148 irradiated patients versus 2480 nonirradiated patients [62].

2.4.2. *Chemotherapy*

Chemotherapy alone rarely produces durable complete responses (CR) of the primary tumour. In general, a clinical CR rate of up to 56%, as reported in some series, must be weighed against a staging error of >60% [5,8]. Response to chemotherapy is a prognostic factor for treatment outcome and eventual survival [2], though it may be confounded by patient selection. Several groups have reported the effect of chemotherapy on resectable tumours (neoadjuvant approach) as well as nonresectable primary tumours [4,63,64]. Two to three cycles of methotrexate, vinblastine, adriamycin, and cisplatin (M-VAC) or gemcitabine and cisplatin (GC) achieved not only downstaging of the primary tumour but also pathologic CRs of bladder primary tumours in 12–50% of patients after M-VAC and in 12–22% of patients after GC in phase 2 and phase 3 trials [4,63,65].

Contemporary series with GC followed by RC reported inferior pT0 rates, which may have been related to a low dose density and inappropriate delay of surgery [66]. As for bladder preservation, a response is evaluated by cystoscopy and computed tomography imaging only, followed by close surveillance. This approach is prone to an imminent staging error, which can put the patient at risk for local recurrence and/or consecutive metastatic disease. For highly selected patients, a bladder-conserving strategy with transurethral resection of the bladder and systemic cisplatin-based chemotherapy—preferably with M-VAC—may allow long-term survival with an intact bladder [11]. However, this approach cannot be recommended for routine use.

3. Metastatic bladder cancer

Advanced BCa is a chemosensitive tumour. Response rates differ with respect to patient-related factors and pretreatment disease. Prognostic factors for response and survival have been established [67–71]. A major prognostic factor is the suitability of patients for treatment with a cisplatin-based combination chemotherapy. Cisplatin remains the most effective single agent for treatment of UC.

Factors preventing patients from receiving cisplatin at any dose include age; obstructing disease; chronic upper tract inflammation; or metabolic changes subsequent to bowel interposition after cystectomy, general health status, and/or poor renal function. Patients are categorised into "fit" or "unfit" for the purpose of receiving cisplatin-containing combination chemotherapy [72] (Table 7).

3.1. *Standard first-line chemotherapy for "fit" patients*

The use of M-VAC and GC both result in prolonged survival of up to 14.8 and 13.8 mo, respectively, also with long-term follow-up [73–76]. The lower toxicity of GC, however, has resulted in GC increasingly becoming a new standard regimen [75].

Although all disease sites have been shown to respond to cisplatin-based combination chemotherapy, most studies have reported the response in lymph nodes. A response rate of 66% and 77% with M-VAC and high-dose (HD)–M-VAC,

Table 7 – Chemotherapy in metastatic bladder cancer

Recommendation:	GR
Standard first-line chemotherapy for "fit" patients:	
First-line treatment for cisplatin-eligible patients ("fit") is cisplatin-containing combination chemotherapy with GC or M-VAC.	A
Chemotherapy in patients ineligible ("unfit") for cisplatin:	
For cisplatin-ineligible patients ("unfit") with either a PS 2 or impaired renal function or with 0–1 poor Bajorin prognostic factors, first-line treatment is carboplatin-containing combination chemotherapy, preferably with Carbo/Gem.	A
Second-line chemotherapy:	
In patients progressing after platinum-based combination chemotherapy for metastatic disease, a trial of vinflunine should be offered, which has the highest LE to date, or clinical trials of other treatments.	A*

GR = grade of recommendation; GC = gemcitabine and cisplatin; M-VAC = methotrexate, vinblastine, adriamycin, and cisplatin; PS = performance status; Carbo/Gem = carboplatin and gemcitabine; LE = level of evidence.
* Grade A recommendation is weakened by a problem of statistical significance.

respectively, has been reported in retroperitoneal lymph nodes versus 29% and 33% at extranodal sites [77,78].

The sites of disease also affect long-term survival. In lymph node–only disease, 20.9% of patients were alive at 5 yr compared to only 6.8% of patients with visceral metastases [76]. To date, further intensification of treatment using new triplets, dose-dense schedules, or adding targeted therapies has not proven superior to GC or M-VAC and is still being investigated [79,80]. The recommendation for first-line treatment for fit patients remains cisplatin-containing combination chemotherapy with GC or M-VAC, preferably with granulocyte-stimulating colony factor (GSCF) or HD-M-VAC with GCSF (Table 7).

3.2. Chemotherapy in patients ineligible ("unfit") for cisplatin

Up to 50% of patients are ineligible for cisplatin-containing chemotherapy, either because of a poor PS and/or impaired renal function or because of comorbidity preventing high-volume hydration. The first randomised phase 2/3 trial in this setting was conducted by the European Organisation for Research and Treatment of Cancer and compared methotrexate, carboplatin, and vinblastine (M-CAVI) and carboplatin and gemcitabine (Carbo/Gem) in patients unfit for cisplatin. Both regimens were active. Severe acute toxicity (SAT) was 13.6% in patients given Carbo/Gem versus 23% on M-CAVI, while the overall response rate was 42% on Carbo/Gem and 30% on M-CAVI. Further analysis showed that combination chemotherapy provides limited benefit in patients with PS 2 and impaired renal function [81]. The overall response rate and SAT were both 26% for the former group and 20% and 24%, respectively, for the latter group [81]. Recent phase 3 data have confirmed these results.

3.3. Second-line chemotherapy

Second-line chemotherapy data are highly variable in this setting. Vinflunine is a novel, third-generation vinca alkaloid that has shown objective response rates of 18% and disease control in 67% of trial subjects [82]. A phase 3 trial of vinflunine plus best supportive care (BSC) randomised against BSC alone in patients progressing after first-line treatment with platinum-containing combination chemotherapy for metastatic disease was recently published [83]. The results showed modest activity (overall response rate: 8.6%), a clinical benefit with a favourable safety profile, and—most importantly—a survival benefit in favour of vinflunine that was statistically significant in the eligible patient population (not in the intention-to-treat population). For second-line treatment in this clinical setting, this trial reached the highest level of evidence reported to date. Currently, vinflunine is the only approved second-line treatment; any other treatment should take place in the context of clinical trials (Table 7).

3.4. Biomarkers

Statistically, relatively modest disease control rates but (sporadically) remarkable responses in some patients with urothelial BCa have led to investigation of biomarkers for assessment of prognosis after surgery and as an indication for chemotherapy or for its monitoring. Most of the biomarkers were associated with tumour angiogenesis. To date, small studies—usually retrospective—have investigated microvessel density, altered p53 tumour expression [84], serum vascular endothelial growth factor [85], urinary and tissue basic fibroblast growth factor (bFGF) [86], urinary (wild type and mutant) and tissue FGF receptor-3 [87], and—more recently—thrombospondin-1 [88], the detection of circulating tumour cells [89], and multidrug-resistance gene expression [90]. Although a few biomarkers have shown potential, none has sufficient evidence to support its routine clinical use (LE: 3; Table 8).

Table 8 – Recommendation on the use of biomarkers

Recommendation	GR
Currently, no biomarkers can be recommended in daily clinical practice because they have no impact on predicting outcome, treatment decisions, or monitoring therapy in invasive BCa.	A*

GR = grade of recommendation; BCa = bladder cancer.
* Upgraded following panel consensus.

Table 9 – Recommendation on supportive therapy

Recommendation:	GR
Patients with metastatic bone disease should receive bisphosphonate treatment.	A

GR = grade of recommendation.

3.5. Bisphosphonates

The prevalence of metastatic bone disease (MBD) in patients with advanced/metastatic UC has been reported as 30–40% [70]. Skeletal complications resulting from MBD have a detrimental effect on pain and QoL and are also associated with increased mortality. Bisphosphonates reduce and delay skeletal-related events (SRE) from bone metastases by inhibiting bone absorption. Bisphosphonate treatment should therefore be considered for all patients with MBD, irrespective of cancer type [91] (Table 9).

To date, only one published randomised, placebo-controlled phase 3 trial has confirmed the beneficial effect of zoledronic acid in treating bone metastases from UC. UC patients treated with zoledronic acid experienced a decrease in SREs and an improvement in their QoL and 1-yr OS. Zoledronic acid is the only bisphosphonate that has been studied [92,93] and approved for the treatment of MBD in all tumour types (LE: 2). Bisphosphonate treatment should be accompanied by calcium and vitamin D supplementation. Dosing regimens should follow respective regulatory recommendations and be adjusted according to preexisting medical conditions.

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Study concept and design: Stenzl.
Acquisition of data: Stenzl, Cowan, Ribal, Kuczyk, Merseburger, De Santis, Sherif, Witjes.
Analysis and interpretation of data: Stenzl, Cowan, Ribal, Kuczyk, Merseburger, De Santis, Sherif, Witjes.
Drafting of the manuscript: Stenzl.
Critical revision of the manuscript for important intellectual content: Stenzl, Cowan, Ribal, Kuczyk, Merseburger, De Santis, Sherif, Witjes.
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