European Association of Urology

Guidelines

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

Arnulf Stenzl[a,*], Nigel C. Cowan[b], Maria De Santis[c], Markus A. Kuczyk[d], Axel S. Merseburger[d], Maria José Ribal[e], Amir Sherif[f], J. Alfred Witjes[g]

[a] Department of Urology, Eberhard-Karls-University Tuebingen, Tuebingen, Germany
[b] Department of Radiology, The Churchill Hospital, Oxford, United Kingdom
[c] 3rd Medical Department and ACR-ITR/CEADDP and LBI-ACR Vienna-CTO, Kaiser Franz Josef Spital, Vienna, Austria
[d] Department of Urology and Urologic Oncology, Hannover Medical School (MHH), Hannover, Germany
[e] Department of Urology, Hospital Clinic, University of Barcelona, Barcelona, Spain
[f] Department of Urology, Karolinska University Hospital, Stockholm, Sweden
[g] Department of Urology, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands

Article info

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 contra-indications, 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.

© 2011 European Association of Urology. Published by Elsevier B.V. All rights reserved.

* Corresponding author. Department of Urology, Eberhard-Karls-University Tuebingen, Hoppe-Seyler-Str. 3, 72076 Tuebingen, Germany. Tel. +49 7071 2986613; Fax: +49 7071 295092.
E-mail address: Urologie@med.uni-tuebingen.de (A. Stenzl).

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

	LE
Conclusions:	
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

	LE
Definitive EBRT	
Conclusion:	
Previously irradiated patients undergoing RC later on have a higher risk of early complications.	3
Recommendations:	
Definitive EBRT:	GR
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

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.

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).

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.

References

[1] Oxford Centre for Evidence-based Medicine – levels of evidence (March 2009). Centre for Evidence-based Medicine Web site. http://www.cebm.net/index.aspx?o=1025. Updated March 2009.

[2] Sternberg CN, Pansadoro V, Calabro F, et al. Can patient selection for bladder preservation be based on response to chemotherapy? Cancer 2003;97:1644–52.

[3] Sanchez-Ortiz RF, Huang WC, Mick R, Van Arsdalen KN, Wein AJ, Malkowicz AB. An interval longer than 12 weeks between the diagnosis of muscle invasion and cystectomy is associated with worse outcome in bladder carcinoma. J Urol 2003;169:110–5, discussion 115.

[4] Stein JP. Contemporary concepts of radical cystectomy and the treatment of bladder cancer. J Urol 2003;169:116–7.

[5] Grossman HB, Natale RB, Tangen CM, et al. Neoadjuvant chemotherapy plus cystectomy compared with cystectomy alone for locally advanced bladder cancer. N Engl J Med 2003;349:859–66.

[6] Sherif A, Holmberg L, Rintala E, et al. Neoadjuvant cisplatinum based combination chemotherapy in patients with invasive bladder cancer: a combined analysis of two Nordic studies. Eur Urol 2004;45:297–303.

[7] Advanced Bladder Cancer (ABC) Meta-analysis Collaboration. Adjuvant chemotherapy in invasive bladder cancer: a systematic review and meta-analysis of individual patient data. Eur Urol 2005;48:189–201, discussion 199–201.

[8] Herr HW, Bajorin DF, Scher HI. Neoadjuvant chemotherapy and bladder-sparing surgery for invasive bladder cancer: ten-year outcome. J Clin Oncol 1998;16:1298–301.

[9] Widmark A, Flodgren P, Damber JE, Hellsten S, Cavallin-Stahl E. A systematic overview of radiation therapy effects in urinary bladder cancer. Acta Oncol 2003;42:567–81.

[10] Granfors T, Tomic R, Ljungberg B. Downstaging and survival benefits of neoadjuvant radiotherapy before cystectomy for patients with invasive bladder carcinoma. Scand J Urol Nephrol 2009;43:293–9.

[11] Rödel C, Weiss C, Sauder R. Trimodality treatment and selective organ preservation for bladder cancer. J Clin Oncol 2006;24:5536–44.

[12] Hautmann RE, Abol-Enein H, Hafez K, et al. Urinary diversion, WHO Consensus Conference on Bladder Cancer. Urology 2007;69(Suppl 1): 17–49.

[13] Stenzl A, Nagele U, Kuczyk M, et al. Cystectomy – technical considerations in male and female patients. EAU Update Series 2005; 3:138–46.

[14] Abdelhady M, Abusamra A, Pautler SE, Chin JL, Izawa JI. Clinically significant prostate cancer found incidentally in radical cystoprostatectomy specimens. BJU Int 2007;99:326–9.

[15] Pettus JA, Al-Ahmadie H, Barocas DA, et al. Risk assessment of prostatic pathology in patients undergoing radical cystoprostatectomy. Eur Urol 2008;53:370–5.

[16] Weizer AZ, Shah RB, Lee CT, et al. Evaluation of the prostate peripheral zone/capsule in patients undergoing radical cystoprostatectomy: defining risk with prostate capsule sparing cystectomy. Urol Oncol 2007;25:460–4.

[17] Gakis G, Schilling D, Bedke J, Sievert KD, Stenzl A. Incidental prostate cancer at radical cystoprostatectomy: implications for apex-sparing surgery. BJU Int 2010;105:468–71.

[18] Ong CH, Schmitt M, Thalmann GN, Studer UE. Individualized seminal vesicle sparing cystoprostatectomy combined with ileal orthotopic bladder substitution achieves good functional results. J Urol 2010;183:1337–41.

[19] Colombo R, Hautmann RE. Open to debate. The motion: seminal-nerve sparing radical cystectomy is an efficacious and safe treatment for selected bladder cancer patients. Eur Urol 2008;53:203–7.

[20] Stenzl A, Colleselli K, Poisel S, Feichtinger H, Pontasch H, Bartsch G. Rationale and technique of nerve sparing radical cystectomy before an orthotopic neobladder procedure in women. J Urol 1995;154:2044–9.

[21] Gakis, G, Schilling D, Perner S, Schwentner C, Sievert KD, Stenzl A. Sequential resection of malignant ureteral margins at radical cystectomy: a critical assessment of the value of frozen section analysis. World J Urol. In press. DOI:10.1007/s00345-010-0581-z.

[22] Tollefson MK, Blute ML, Farmer SA, Frank I. Significance of distal ureteral margin at radical cystectomy for urothelial carcinoma. J Urol 2010;183:81–6.

[23] Schumacher MC, Scholz M, Weise ES, Fleischmann A, Thalmann GN, Studer UE. Is there an indication for frozen section examination of the ureteral margins during cystectomy for transitional cell carcinoma of the bladder? J Urol 2006;176:2409–13, discussion 2413.

[24] Herr HW, Bochner BH, Dalbagni G, Donat SM, Reuter VE, Bajorin DF. Impact of the number of lymph nodes retrieved on outcome in patients with muscle invasive bladder cancer. J Urol 2002;167: 1295–8.

[25] Leissner J, Hohenfellner R, Thuroff JW, Wolf HK. Lymphadenectomy in patients with transitional cell carcinoma of the urinary bladder; significance for staging and prognosis. BJU Int 2000;85:817–23.

[26] Poulsen AL, Horn T, Steven K. Radical cystectomy: extending the limits of pelvic lymph node dissection improves survival for patients with bladder cancer confined to the bladder wall. J Urol 1998;160:2015–9, discussion 2020.

[27] Ghoneim MA, Abol-Enein H. Lymphadenectomy with cystectomy: is it necessary and what is its extent? Eur Urol 2004; 46:457–61.

[28] Roth B, Wissmeyer MP, Zehnder P, et al. A new multimodality technique accurately maps the primary lymphatic landing sites of the bladder. Eur Urol 2010;57:205–11.

[29] Pruthi RS, Nix J, McRackan D, et al. Robotic-assisted laparoscopic intracorporeal urinary diversion. Eur Urol 2010;57:1013–21.

[30] Hautmann RE. The oncologic results of laparoscopic radical cystectomy are not (yet) equivalent to open cystectomy. Curr Opin Urol 2009;19:522–6.

[31] Haber G-P, Crouzet S, Gill IS. Laparoscopic and robotic assisted radical cystectomy for bladder cancer: a critical analysis. Eur Urol 2008;54:54–64.

[32] Gakis G, Stenzl A. Ileal neobladder and its variants. Eur Urol Suppl 2010;9:745–53.

[33] Pycha A, Comploj E, Martini T, et al. Comparison of complications in three incontinent urinary diversions. Eur Urol 2008;54:825–32.

[34] Nieuwenhuijzen JA, de Vries RR, Bex A, et al. Urinary diversions after cystectomy: the association of clinical factors, complications and functional results of four different diversions. Eur Urol 2008;53:834–44, discussion 842–4.

[35] Farnham SB, Cookson MS. Surgical complications of urinary diversion. World J Urol 2004;22:157–67.

[36] Stenzl A, Sherif H, Kuczyk M. Radical cystectomy with orthotopic neobladder for invasive bladder cancer: a critical analysis of long term oncological, functional and quality of life results. Int Braz J Urol 2010;36:537–47.

[37] Stein JP, Clark P, Miranda G, Cai J, Groshen S, Skinner DG. Urethral tumor recurrence following cystectomy and urinary diversion: clinical and pathological characteristics in 768 male patients. J Urol 2005;173:1163–8.

[38] Hautmann RE, Volkmer BG, Schumacher MC, Gschwend JE, Studer UE. Long-term results of standard procedures in urology: the ileal neobladder. World J Urol 2006;24:305–14.

[39] Froehner M, Brausi MA, Herr HW, Muto G, Studer UE. Complications following radical cystectomy for bladder cancer in the elderly. Eur Urol 2009;56:443–54.

[40] Gschwend JE, Dahm P, Fair WR. Disease specific survival as endpoint of outcome for bladder cancer patients following radical cystectomy. Eur Urol 2002;41:440–8.

[41] Shariat SF, Karakiewicz PI, Palapattu GS, et al. Nomograms provide improved accuracy for predicting survival after radical cystectomy. Clin Cancer Res 2006;12:6663–76.

[42] Zaak D, Burger M, Otto W, et al. Predicting individual outcomes after radical cystectomy: an external validation of current nomograms. BJU Int 2010;106:342–8.

[43] Stein JP, Lieskovsky G, Cote R, et al. Radical cystectomy in the treatment of invasive bladder cancer: long-term results in 1,054 patients. J Clin Oncol 2001;19:666–75.

[44] Madersbacher S, Hochreiter F, Burkhard F, et al. Radical cystectomy for bladder cancer today—a homogeneous series without neoadjuvant therapy. J Clin Oncol 2003;21:690–6.

[45] Hollenbeck BK, Miller DC, Taub D, et al. Aggressive treatment for bladder cancer is associated with improved overall survival among patients 80 years old or older. Urology 2004;64:292–7.

[46] Lodde M, Palermo S, Comploj E, et al. Four years experience in bladder preserving management for muscle invasive bladder cancer. Eur Urol 2005;47:773–9.

[47] Nagele U, Anastasiadis AG, Merseburger AS, et al. The rationale for radical cystectomy as primary therapy for T4 bladder cancer. World J Urol 2007;25:401–5.

[48] Lawrentschuk N, Colombo R, Hakenberg OW, et al. Prevention and management of complications following radical cystectomy for bladder cancer. Eur Urol 2010;57:983–1001.

[49] Konety BR, Dhawan V, Allareddy V, O'Donnell MA. Association between volume and charges for most frequently performed ambulatory and nonambulatory surgery for bladder cancer. Is more cheaper? J Urol 2004;172:1056–61.

[50] Hautmann RE, de Petriconi RC, Volkmer BG. Lessons learned from 1,000 neobladders: the 90-day complication rate. J Urol 2010;184: 990–4, quiz 1235.

[51] Shamim Khan M, Elhage O, et al. Analysis of early complications of robotic-assisted radical cystectomy using a standardized reporting system. Urology 2011;77:357–62.

[52] Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 2004;240:205–13.

[53] Svatek RS, Fisher MB, Matin SF, et al. Risk factor analysis in a contemporary cystectomy cohort using standardized reporting methodology and adverse event criteria. J Urol 2010;183:929–34.

[54] Donat SM. Standards for surgical complication reporting in urologic oncology: time for a change. Urology 2007;69:221–5.

[55] Novara G, De Marco V, Aragona M, et al. Complications and mortality after radical cystectomy for bladder transitional cell cancer. J Urol 2009;182:914–21.

[56] De Neve W, Lybeert ML, Goor C, Crommelin MA, Ribot JG. Radiotherapy for T2 and T3 carcinoma of the bladder: the influence of overall treatment time. Radiother Oncol 1995;36:183–8.

[57] Mameghan H, Fisher R, Mameghan J, Brook S. Analysis of failure following definitive radiotherapy for invasive transitional cell carcinoma of the bladder. Int J Radiat Oncol Biol Phys 1995;31:247–54.

[58] Näslund I, Nilsson B, Littbrand B. Hyperfractionated radiotherapy of bladder cancer. A ten-year follow-up of a randomized clinical trial. Acta Oncol 1994;33:397–402.

[59] Tonoli S, Bertoni F, De Stefani A, et al. Radical radiotherapy for bladder cancer: retrospective analysis of a series of 459 patients treated in an Italian institution. Clin Oncol (R Coll Radiol) 2006;18:52–9.

[60] Shelley MD, Barber J, Wilt T, Mason MD. Surgery versus radiotherapy for muscle invasive bladder cancer. Cochrane Database Syst Rev 2002, CD002079.

[61] Piet AH, Hulshof MC, Pieters BR, Pos FJ, de Reijke TM, Koning CC. Clinical results of a concomitant boost radiotherapy technique for muscle-invasive bladder cancer. Strahlenther Onkol 2008;184: 313–8.

[62] Eisenberg MS, Dorin RP, Bartsch G, Cai J, Miranda G, Skinner EC. Early complications of cystectomy after high dose pelvic radiation. J Urol 2010;184:2264–9.

[63] Kachni LA, Kaufman DS, Heney NM, et al. Bladder preservation by combined modality therapy for invasive bladder cancer. J Clin Oncol 1997;15:1022–9.

[64] Als AB, Sengelov L, von der Maase H. Long-term survival after gemcitabine and cisplatin in patients with locally advanced transitional cell carcinoma of the bladder: focus on supplementary treatment strategies. Eur Urol 2007;52:478–87.

[65] Advanced Bladder Cancer (ABC) Meta-analysis Collaboration. Neoadjuvant chemotherapy in invasive bladder cancer: update

of a systematic review and meta-analysis of individual patient data. Eur Urol 2005;48:202–6, discussion 205–6.

[66] Weight CJ, Garcia JA, Hansel DE, et al. Lack of pathologic downstaging with neoadjuvant chemotherapy for muscle-invasive urothelial carcinoma of the bladder: a contemporary series. Cancer 2009;115:792–9.

[67] Loehrer Sr PJ, Einhorn LH, Elson PJ, et al. A randomized comparison of cisplatin alone or in combination with methotrexate, vinblastine, and doxorubicin in patients with metastatic urothelial carcinoma: a cooperative group study. J Clin Oncol 1992;10:1066–73.

[68] Bajorin DF, Dodd PM, Mazumdar M, et al. Long-term survival in metastatic transitional-cell carcinoma and prognostic factors predicting outcome of therapy. J Clin Oncol 1999;17:3173–81.

[69] Bellmunt J, Albanell J, Paz-Ares L, et al. Pretreatment prognostic factors for survival in patients with advanced urothelial tumors treated in a phase I/II trial with paclitaxel, cisplatin, and gemcitabine. Cancer 2002;95:751–7.

[70] Bajorin D. The phase III candidate: can we improve the science of selection? J Clin Oncol 2004;22:211–3.

[71] Bellmunt J, Choueiri TK, Fougeray R, et al. Prognostic factors in patients with advanced transitional cell carcinoma of the urothelial tract experiencing treatment failure with platinum-containing regimens. J Clin Oncol 2010;28:1850–5.

[72] De Santis M, Bachner M. New developments in first- and second-line chemotherapy for transitional cell, squamous cell and adenocarcinoma of the bladder. Curr Opin Urol 2007;17:363–8.

[73] Sternberg CN, Yagoda A, Scher HI, et al. Methotrexate, vinblastine, doxorubicin, and cisplatin for advanced transitional cell carcinoma of the urothelium. Efficacy and patterns of response and relapse. Cancer 1989;64:2448–58.

[74] Sternberg CN, Yagoda A, Scher HI, et al. M-VAC (methotrexate, vinblastine, doxorubicin and cisplatin) for advanced transitional cell carcinoma of the urothelium. J Urol 1988;139:461–9.

[75] von der Maase H, Hansen SW, Roberts JT, et al. Gemcitabine and cisplatin versus methotrexate, vinblastine, doxorubicin, and cisplatin in advanced or metastatic bladder cancer: results of a large, randomized, multinational, multicenter, phase III study. J Clin Oncol 2000;18:3068–77.

[76] von der Maase H, Sengelov L, Roberts JT, et al. Long-term survival results of a randomized trial comparing gemcitabine plus cisplatin, with methotrexate, vinblastine, doxorubicin, plus cisplatin in patients with bladder cancer. J Clin Oncol 2005;23:4602–8.

[77] Sternberg CN, de Mulder PH, Schornagel JH, et al., European Organization for Research and Treatment of Cancer Genitourinary Tract Cancer Cooperative Group. Randomized phase III trial of high-dose-intensity methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) chemotherapy and recombinant human granulocyte colony-stimulating factor versus classic MVAC in advanced urothelial tract tumors: European Organization for Research and Treatment of Cancer Protocol no. 30924. J Clin Oncol 2001;19:2638–46.

[78] Sternberg CN, de Mulder P, Schornagel JH, et al. Seven year update of an EORTC phase III trial of high-dose intensity M-VAC chemotherapy and G-CSF versus classic M-VAC in advanced urothelial tract tumours. Eur J Cancer 2006;42:50–4.

[79] Milowsky MI, Nanus DM, Maluf FC, et al. Final results of sequential doxorubicin plus gemcitabine and ifosfamide, paclitaxel, and cisplatin chemotherapy in patients with metastatic or locally advanced transitional cell carcinoma of the urothelium. J Clin Oncol 2009;27:4062–7.

[80] Hussain MH, MacVicar GR, Petrylak DP, et al. Trastuzumab, paclitaxel, carboplatin, and gemcitabine in advanced human epidermal growth factor receptor-2/neu-positive urothelial carcinoma: results of a multicenter phase II National Cancer Institute trial. J Clin Oncol 2007;25:2218–24.

[81] De Santis M, Bellmunt J, Mead G, et al. Randomized phase II/III trial assessing gemcitabine/carboplatin and methotrexate/carboplatin/vinblastine in patients with advanced urothelial cancer "unfit" for cisplatin-based chemotherapy: phase II—results of EORTC study 30986. J Clin Oncol 2009;27:5634–9.

[82] Culine S, Theodore C, De Santis M. A phase II study of vinflunine in bladder cancer patients progressing after first-line platinum-containing regimen. Br J Cancer 2006;94:1395–401.

[83] Bellmunt J, Theodore C, Demkov T, et al. Phase III trial of vinflunine plus best supportive care compared with best supportive care alone after a platinum-containing regimen in patients with advanced transitional cell carcinoma of the urothelial tract. J Clin Oncol 2009;27:4454–61.

[84] Youssef RF, Mitra AP, Bartsch Jr G, Jones PA, Skinner DG, Cote RJ. Molecular targets and targeted therapies in bladder cancer management. World J Urol 2009;27:9–20.

[85] Shariat SF, Youssef RF, Gupta A, et al. Association of angiogenesis related markers with bladder cancer outcomes and other molecular markers. J Urol 2010;183:1744–50.

[86] Song S, Wientjes MG, Gan Y, Au JL. Fibroblast growth factors: an epigenetic mechanism of broad spectrum resistance to anticancer drugs. Proc Natl Acad Sci U S A 2000;97:8658–63.

[87] Gomez-Roman JJ, Saenz P, Molina M, et al. Fibroblast growth factor receptor 3 is overexpressed in urinary tract carcinomas and modulates the neoplastic cell growth. Clin Cancer Res 2005;11:459–65.

[88] Ioachim E, Michael MC, Salmas M, et al. Thrombospondin-1 expression in urothelial carcinoma: prognostic significance and association with p53 alterations, tumour angiogenesis and extracellular matrix components. BMC Cancer 2006;6:140.

[89] Gallagher DJ, Milowsky MI, Ishill N, et al. Detection of circulating tumor cells in patients with urothelial cancer. Ann Oncol 2009;20:305–8.

[90] Hoffmann AC, Wild P, Leicht C, et al. MDR1 and ERCC1 expression predict outcome of patients with locally advanced bladder cancer receiving adjuvant chemotherapy. Neoplasia 2010;12:628–36.

[91] Aapro M, Abrahamsson PA, Body JJ, et al. Guidance on the use of bisphosphonates in solid tumours: recommendations of an international expert panel. Ann Oncol 2008;19:420–32.

[92] Zaghloul MS, Boutrus R, El-Hossieny H, Kader YA, El-Attar I, Nazmy M. A prospective, randomized, placebo-controlled trial of zoledronic acid in bony metastatic bladder cancer. Int J Clin Oncol 2010;15:382–9.

[93] Rosen LS, Gordon D, Tchekmedyian NS, et al. Long-term efficacy and safety of zoledronic acid in the treatment of skeletal metastases in patients with nonsmall cell lung carcinoma and other solid tumors: a randomized, phase III, double-blind, placebo-controlled trial. Cancer 2004;100:2613–21.