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European Association of Urology

Review – Bladder Cancer

The Updated EAU Guidelines on Muscle-Invasive and Metastatic Bladder Cancer

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Abstract

Context: New data regarding diagnosis and 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.

Evidence acquisition: A comprehensive workup of the literature obtained from Medline, the Cochrane central register of systematic reviews, and reference lists in publications and review articles was developed and screened by a group of urologists, oncologists, and radiologist appointed by the EAU Guideline Committee. Previous recommendations based on the older literature on this subject were taken into account. Levels of evidence and grade of guideline recommendations were added, modified from the Oxford Centre for Evidence-based Medicine Levels of Evidence.

Evidence synthesis: The diagnosis of muscle-invasive bladder cancer (BCa) is made by transurethral resection (TUR) and following histopathologic evaluation. Patients with confirmed muscle-invasive BCa should be staged by computed tomography (CT) scans of the chest, abdomen, and pelvis, if available. Adjuvant chemotherapy is currently only advised within clinical trials. Radical cystectomy (RC) is the treatment of choice for both sexes, and lymph node dissection should be an integral part of

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cystectomy. 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. 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 clinical or personal reasons. An appropriate schedule for disease monitoring should be based on (1) natural timing of recurrence, (2) probability of disease recurrence, (3) functional deterioration at particular sites, and (4) consideration of treatment of a recurrence. In metastatic disease, the first-line treatment for patients fit enough to sustain cisplatin is cisplatin-containing combination chemotherapy. Presently, there is no standard second-line chemotherapy.
Conclusions: These EAU guidelines are a short, comprehensive overview of the updated guidelines of (MiM-BC) as recently published in the EAU guidelines and also available in the National Guideline Clearinghouse.

1. Introduction

Publications concerning muscle-invasive and metastatic bladder cancer (MiM-BC) are mostly based on retrospective analyses, including some larger multicentre studies and well-designed controlled studies. Few randomised studies are available on the diagnosis and surgical treatment of MiM-BC, and qualified, evidence-based data for many important clinical aspects do not reach levels usually obtained in some of the medical areas.

2. Methods

The recommendations provided in the current guidelines are based on a systemic literature search using Medline, the Cochrane Central Register of Systematic Reviews, and reference lists in publications and review articles. Previous recommendations on MiM-BC have been taken into account [1].

A thorough workup of the literature referenced in Medline and other public databases since the last update of MiM-BC was performed. Based on this workup, all members composed the conclusions and recommendations of each chapter. Levels of evidence and grade of guideline recommendations were added based on the Oxford Centre for Evidence-based Medicine Levels of Evidence [2]. The aim of grading the recommendations is to provide transparency between the underlying evidence and the recommendation given. Subsequently, the most important conclusions, with a particular emphasis on changes to previous published versions of the guidelines with level of evidence (LE: 1–4; Table 1) and recommendations with grade (A–C; Table 1), are outlined.

2.1. *Epidemiology and risk factors*

In 2006 in Europe, an estimated 104 400 incident cases of bladder cancer (BCa) were diagnosed (82 800 in men and 21 600 in women), which represents 6.6% of the total cancers in men and 2.1% in women. The estimated ratio by gender was 3.8:1, respectively. In men, BCa was the fourth most common cancer. BCa represents 4.1% of total deaths for cancer in men and 1.8% of total deaths in women [3].

Tobacco smoking remains the most well-established risk factor for BCa, causing around 50–65% of male cases and 20–30% of female cases. Occupational exposure has been considered the second most important risk factor for BCa. Work-related cases account for 20–25% of all BCa cases in several series, with a trend to decrease in recent series [4]. Increased rates of secondary bladder malignancies have been reported after external beam radiation therapy (EBRT) for gynaecologic malignancies, with relative risks of 2–4 [5]; in

Table 1 – Levels of evidence and grade of guideline recommendations as used by the European Association of Urology modified from Sackett et al [2]

Level	Type of evidence
1a	Evidence obtained from meta-analysis of randomised trials
1b	Evidence obtained from at least one randomised trial
2a	Evidence obtained from one well-designed controlled study without randomisation
2b	Evidence obtained from at least one other type of well-designed quasiexperimental study
3	Evidence obtained from well-designed nonexperimental studies, such as comparative studies, correlation studies, and case reports
4	Evidence obtained from expert committee reports or opinions or clinical experience of respected authorities
Grade	Nature of recommendations
A	Based on clinical studies of good quality and consistency addressing the specific recommendations and including at least one randomised trial
B	Based on well-conducted clinical studies but without randomised clinical trials
C	Made despite the absence of directly applicable clinical studies of good quality

patients treated for prostate cancer (PCa), the incidence of BCa was significantly lower in patients treated with radical prostatectomy (RP) than in patients who underwent EBRT [6]. Differences in the gender prevalence of BCa seem to be the result of causes other than tobacco and chemical exposure [7,8].

2.2. *Classification and grading*

The 2002 TNM classification approved by the Union International Contre le Cancer (UICC) has been widely accepted and is the basis for the current guidelines [9]. The use of the 2004 World Health Organisation (WHO) classification is advocated, as it should result in a uniform diagnosis of tumours [10]. However, until the 2004 WHO classification has been validated by more clinical trials, tumours should be graded using both the 1973 and the 2004 WHO classifications. The majority of clinical trials published so far have been performed using the 1973 WHO classification; therefore, the following guidelines are based on the 1973 WHO grade classification.

2.3. *Diagnostic procedures*

Bimanual examination should be carried out before and after transurethral resection (TUR) to assess whether there is a palpable mass or the tumour is fixed to the pelvic wall [11,12]. If invasive BCa is suspected at cystoscopy, the appropriate imaging studies should be performed before TUR. After TUR, it is impossible to discriminate between inflammatory reaction and tumour growth in the perivesical fat [13].

Multidetector computed tomography urography (MDCTU) is the preferred imaging modality for diagnosis and staging of upper urinary tract and bladder cancer (Table 2). MDCTU can be used as an alternative to intravenous urography (IVU) [14] for invasive tumours of the upper tract, because it provides more information than IVU (LE: 4), but MDCTU has the disadvantage of a higher radiation exposure than IVU.

IVU may detect large tumours as filling defects or deformation in the bladder outline. IVU may also depict signs of a ureteral tumour seen as filling defects in the upper urinary tract and hydronephrosis. The necessity of performing routine IVU in patients with known bladder tumour is now questioned because of the low incidence of significant findings obtained with this method [14,15] (LE: 3). The incidence of upper urinary tract tumours is low (1.8%) but increases to 7.5 % in tumours located in the trigone [16].

Transabdominal ultrasonography permits characterisation of large renal masses, detection of hydronephrosis, and visualisation of intraluminal filling defects in the bladder. Combined with plain abdominal film, it can be as accurate as IVU in diagnosing the cause of haematuria [17] (LE: 3).

In experienced hands, examination, urinary cytology, and urinary markers yield a sensitivity and specificity in excess of 90% in high-grade tumours or if carcinoma in situ (CIS) is present [18,19] (LE: 2b). It is thus particularly useful for muscle-invasive BCa, because most invasive tumours are high grade. The same may apply to urinary markers, although none is registered specifically for the diagnosis of invasive BCa.

The diagnosis of BCa ultimately depends on cystoscopy of the bladder and histologic evaluation of the resected tissue. In general, cystoscopy is initially performed in the office, using flexible or rigid instruments. If a bladder tumour has been visualised in imaging studies, such as careful ultrasonography, multidetector computed tomography (MDCT), or magnetic resonance imaging (MRI), diagnostic cystoscopy can be omitted, because the patient will undergo TUR for a histologic diagnosis.

2.3.1. *Transurethral resection of invasive bladder tumours*

The goal of any TUR or re-TUR in invasive bladder tumours is to make the correct diagnosis, which means including bladder muscle in the resection biopsies. The recently published guidelines of non–muscle-invasive BCa can be consulted for further information [20].

2.3.2. *Bladder and prostatic urethra biopsies*

The involvement of the prostatic urethra and ducts in male patients with bladder tumours seems to be higher if the tumour is located on the trigone or bladder neck, in the presence of extensive bladder CIS, and in multifocal tumours [19,20] (LE: 3). In these cases and/or with abnormalities of the prostatic urethra, resection loop biopsies of the precollicular prostatic urethra are recommended (grade of recommendation: C). Special care must be taken with tumours at the bladder neck and trigone in female patients, where urethral preservation for an orthotopic neobladder is planned. Bladder neck biopsies in women are advisable but not mandatory, provided frozen sections at the urethral margin are taken at the time of surgery [21] (LE: 4).

Table 2 – Recommendations for staging in verified bladder tumours

Diagnosis of invasive BCa:
- Cystoscopy and biopsy
- Imaging only if staging will make a difference to the selection of treatment options

Local staging for patients considered suitable for radical treatment (grade of recommendation: B):
- MRI scanning with fast dynamic contrast-enhancement
- MDCT with contrast enhancement

For patients with confirmed muscle-invasive BCa (grade of recommendation: B):
- MDCT of the chest, abdomen, and pelvis, including MDCTU for complete examination of the upper urinary tracts
- Lesser alternatives (eg, if MDCT is not available) are excretory urography and a chest x-ray (grade of recommendation: B)

BCa = bladder cancer; MDCT = multidetector-row computed tomography; MDCTU = multidetector-row computed tomography urography; MRI = magnetic resonance imaging.

2.3.3. *Concomitant prostate cancer*

Investigation for PCa should be done according the EAU guidelines for PCa [22].

3. Staging

3.1. *Imaging in verified bladder tumours*

3.1.1. *Local staging of invasive bladder cancer*

Both computed tomography (CT) and MRI scans can be used for assessment of local invasion [23], but they are unable to detect microscopic invasion of perivesical fat (T3a). The aim of CT and MRI scanning is therefore to detect T3b disease or higher. For the bladder, MRI scanning has superior soft tissue contrast resolution compared with CT scanning but poorer spatial resolution. In studies prior to the availability of MDCT, MRI scanning was reported to be more accurate for local assessment. The accuracy of MRI scans for primary tumour staging varies from 73% to 96% (mean: 85%). These values were 10–33% (mean: 19%) higher than those obtained with CT scanning.

Fast dynamic contrast-enhanced MRI scanning is helpful in the differentiation of bladder tumour from surrounding tissues, because the tumour enhances earlier than the normal bladder wall because of neovascularisation [13]. Fast dynamic MRI scanning with images acquired at one per second helps in distinguishing tumour from postbiopsy reaction [13]. The advantages of CT scanning include shorter acquisition time, wider coverage in a single breath hold, and lower susceptibility to various patient factors. The accuracy of CT scans in determining extravesical tumour extension varies from 55% to 92% [24] and increases with more advanced disease [25].

The accuracy of MDCT for detection and staging of BCa showed lower sensitivity (89% vs 100%) and higher specificity (95% vs 73%) for CT scans compared to MRI scanning for diagnosis of perivesical invasion, whereas the cancer-detection rate and overall accuracy for perivesical invasion were similar [26].

3.2. *Imaging of nodal involvement and distant metastases*

The assessment of nodal status based simply on size is limited by the inability of both CT and MRI scanning to identify metastases in normal-sized or minimally enlarged nodes. Sensitivities for detection of lymph node metastases are low, ranging from 48% to 87%. Specificities are also low, ranging from 64%, as nodal enlargement may be to the result of benign pathology. Overall, the results of CT and MRI scanning for detection of lymph node metastases in a variety of primary pelvic tumours are similar [27,28]. Pelvic nodes >8 mm and abdominal nodes >10 mm in maximum short axis diameter (MSAD) should be regarded as enlarged on CT and MRI scans [14, 28–31].

Prior to any treatment aimed at cure, it is essential to evaluate the presence of distant metastases. MDCT and MRI scans are the diagnostic tools of choice to detect metastases to lung and liver (LE: 2b–3).

Metastasis to bones or brain at presentation of invasive BCa are rare; therefore, bone scan and additional brain imaging are not routinely indicated unless the patient has specific symptoms or signs to suggest bone or brain metastases [14,29]. MRI scanning is more sensitive and specific for diagnosing bone metastases than bone scintigraphy [31,32] (LE: 2b).

4. Localised muscle-invasive bladder cancer

4.1. *Neoadjuvant chemotherapy*

The advantages of neoadjuvant chemotherapy—that is, administering chemotherapy to patients with clinically operable transitional cell carcinoma (TCC) of the urinary bladder before the planned definitive surgery (or radiation)—are manifold: Chemotherapy is delivered at the earliest time point, when the burden of micrometastatic disease is expected to be low; in vivo chemo-sensitivity is tested; and tolerability of chemotherapy is expected to be better before than after cystectomy. However, there are also considerable disadvantages to neoadjuvant chemotherapy. Errors in staging may lead to overtreatment; delayed cystectomy, compromising outcome in patients not sensitive to chemotherapy [33–35]; and side effects of chemotherapy affecting the outcome of surgery and type of urinary diversion [36]. As a result of a 5–8 % overall survival (OS) advantage in recently published studies and meta-analyses, it has therefore been recommended that neoadjuvant cisplatin containing combination chemotherapy should be considered in muscle-invasive BCa irrespective of definitive treatment (grade of recommendation: A) [37–40].

Neoadjuvant chemotherapy is not recommended in patients with a performance score (PS) ≥2 and impaired renal function (grade of recommendation: B). Chemotherapy alone is not recommended as the primary therapy for localised BCa (grade of recommendation: A) [41].

5. Radical surgery and urinary diversion

Radical cystectomy (RC) is currently the standard treatment for localised, muscle-invasive BCa in most countries of the Western hemisphere [42,43]. New interest in quality-of-life (QoL) issues has increased the trend towards preservation of the urethra to make an orthotopic neobladder possible as well as preservation of intrapelvic autonomic nerves to improve potency and continence as well as towards bladder-preservation treatment modalities like radiotherapy (RT) and/ or chemotherapy. PS and age influence the choice of primary therapy for the tumour as well as the type of subsequent urinary diversion [44]. The delay of cystectomy—typically defined as treatment beyond 90 days after diagnosis—affects both outcome and type of urinary diversion [34,45]. See Table 3 for recommendations on cystectomy and urinary diversion.

5.1. *Surgical extent and technique*

RC includes the removal of the bladder and adjacent organs—that is, prostate and seminal vesicles in men and uterus and adnexa in women [46]—and the respective lymph nodes. The inclusion of the entire prostate in male patients and the extent of urethrectomy and vaginal resection in female patients, however, have recently been questioned [47,48]. Various techniques of partial prostate-sparing cystoprostatectomy in male patients with localised tumours have been proposed, and results of a series with a longer follow-up have been published. Autopsy studies as well as studies looking at the unsuspected incidence of PCa in cystoprostatectomy specimens suggest that in approximately 23–54% of patients, PCa is found in the cystoprostatectomy specimen, with up to 29% being clinically significant, locally recurrent, or even metastatic [49–51]. Overall, in some series, only 26–33% of the patients undergoing cystoprostatectomy had neither PCa nor prostatic urothelial cancer.

In retrospective studies, extended lymphadenectomy has been reported to improve survival in patients with muscle-invasive BCa. The curative value of lymph node dissection, however, is still unknown, and a standardised lymph node dissection has yet to be defined [52–54]. There are several localisation studies with regards to lymphadenectomy [55,56] that demonstrated both retrospectively and prospectively that positive lymph nodes in BCa patients are not found outside the pelvis if the pelvic lymph nodes are free of tumour. Furthermore, progression-free survival as well as OS might be correlated with the amount of lymph nodes removed during surgery [53,56].

A distal ureteral segment (length not specified) should be resected and, in specific constellations such as CIS, a frozen section for evaluation of the surgical margins should be performed [46,57]. Urethrectomy is recommended if there are positive margins at the level of urethral dissection (in both sexes), if the primary tumour is located at the bladder neck or in the urethra (in women), or if the tumour extensively infiltrates the prostate [41,43,57].

5.2. *Urinary diversion after radical cystectomy*

From an anatomical standpoint, three alternative forms of diversion—abdominal, urethral, and rectosigmoid—are presently used after cystectomy: Different types of segments of the intestinal tract have been used for reconstruction of the urinary tract, including stomach, ileum, colon, and the appendix [58]. Although several studies have compared certain aspects of health-related QoL, like sexual function, urinary continence, and body image in patient cohorts with different types of urinary diversion, more work is necessary in this

Table 3 – Recommendations for radical cystectomy and urinary diversions in both sexes

- RC in T2–T4a, N0–NX, M0, and high-risk non–muscle-invasive BCa as outlined above (grade of recommendation: B)
- No preoperative RT (grade of recommendation: A)
- Lymph node dissection should be an integral part of cystectomy; extent not established (grade of recommendation: B)
- Preservation of the urethra is reasonable if margins are negative; if no bladder substitution is attached, the urethra must be checked regularly (grade of recommendation: B)
- An orthotopic bladder substitute should be offered to male and female patients lacking any contraindications and who have no tumour in the urethra and at the level of urethral dissection (grade of recommendation: B)
- Laparoscopic and robot-assisted laparoscopic cystectomy may be an option; current data, however, have not sufficiently proven its advantages or disadvantages (grade of recommendation: C)
- Treatment is recommended at centres experienced in major types of diversion techniques and postoperative care (grade of recommendation: B)
- Before cystectomy, the patient should be counselled adequately regarding all possible alternatives, and the final decision should be based on a consensus between patient and surgeon (grade of recommendation: B)

RC = radical cystectomy; RT = radiotherapy.

field with regards to preoperative tumour stage and functional situation, socioeconomic status, time interval to primary surgery, and so forth.

Patients undergoing any type of urinary diversion have to be motivated to learn and be manually skilful to deal with their diversion. Debilitating neurologic and psychiatric illnesses, limited life expectancy, and impaired liver or renal function as well as TCC of the urethral margin or other surgical margins are contraindications to more complex forms of urinary diversion. Relative contraindications specific for an orthotopic neobladder are high-dose preoperative RT, complex urethral stricture disease, and severe urethral sphincter–related incontinence [59–61].

5.3. *Oncologic results of surgery*

Recurrence-free and overall survival in male and female patients is reported as 66–68% and 58–66%, respectively, at 5 yr and 60–73% and 43–49%, respectively, at 10 yr [43]. In node-positive patients, 10-yr disease-specific and overall survival rates were reduced to 27.7% and 20.9%, respectively [62]. These results have as of now not been reached in stage-equivalent large studies with bladder-sparing treatment alternatives (see below). Cystectomy is associated with the greatest risk reduction in disease-related and non–disease-related death in patients older than 80 yr [63]. The largest retrospective single-institution study on cystectomy to date demonstrated that patients above 80 yr of age did have an increased postoperative morbidity but not an increased mortality [64].

Despite the fact that preoperative RT for operable muscle-invasive BCa results in tumour downstaging after 4–6 wk, it is not recommended to improve survival (grade of recommendation: B) [65].

5.4. *Palliative cystectomy for muscle-invasive bladder carcinoma*

In patients with locally advanced pelvic cancer and urinary bladder involvement, palliative RC with urinary diversion using intestinal segments is usually performed for the relief of symptoms such as pain, recurrent bleeding, urgency, and fistula formation [66]. For patients with inoperable locally advanced tumours (T4b), primary RC is not recommended as a curative option (grade of recommendation: B). The only indication for performing a palliative cystectomy is symptom relief, and morbidity of surgery and QoL should be weighed against other options (grade of recommendation: B/C; LE: 3).

5.5. *Bladder-sparing treatment modalities*

TUR alone, RT alone, or chemotherapy alone is not recommended as a curative primary treatment option for the majority of patients with localised BCa (grade of recommendation: B). Successful long-term survival rates in cases of multimodality treatment combining TUR, RT, and chemotherapy have been observed (LE: 3) [41,67–69]. A bladder-preserving multimodality strategy, however, requires very close multidisciplinary cooperation and a high level of patient compliance. Even if a patient has shown a complete response to a multimodality bladder-preserving strategy, the bladder remains a potential source of recurrence. About half of patients can be expected to survive with their native bladder intact. A T0 status at repeat TUR after the initial TUR of the primary tumour followed by chemotherapy in combination with RT was identified as a prognostically important variable [67,70]. However, even the latter patients are at a life-long risk of developing intravesical tumour recurrences, with the need for meticulous surveillance and multiple invasive procedures. It has been postulated that a delay in RC because of an initial bladder-preserving approach increases the risk of lymph node metastases to a lymph node–positive rate of 26% when cystectomy becomes necessary because of treatment failure (LE: 2b). Multimodality treatment in localised disease is currently regarded only as an alternative in selected, well-informed, and compliant patients in whom cystectomy is not considered for clinical or personal reasons (grade of recommendation: B).

6. Chemotherapy in nonlocalised bladder cancer

6.1. *Adjuvant chemotherapy*

To date, there have been only five published randomised trials of adjuvant chemotherapy and one meta-analysis, with updated individual patient data from six trials and a total of only 491 patients for survival analysis [37,71–75].

Furthermore, all these trials are suboptimal with serious deficiencies, such as low sample size (underpowered), use of substandard chemotherapy, early stopping of patient entry, and flaws in design and statistical analysis, including irrelevant end points or a lack of recommendations concerning salvage chemotherapy for relapse or metastases [76]. The data are not convincing enough to give a confounded recommendation for the use of adju-

vant chemotherapy (LE: 1a). Adjuvant chemotherapy is therefore advised within clinical trials only, and not for routine use, because it has not been studied sufficiently (grade of recommendation: A).

6.2. *Chemotherapy in metastatic disease*

BCa is a chemosensitive tumour. Response rates differ with respect to patient-related factors and pretreatment disease. Single-agent chemotherapy provides low response rates of typically short duration (LE: 2a).

Prognostic factors for response and survival have been established [77]. Cisplatin-containing combination chemotherapy has been the standard of care since the late 1980 s. Methotrexate, vinblastine, doxorubicin (Adriamycin), and cisplatin (M-VAC) and gemcitabine/cisplatin (GC) have prolonged survival up to 14.8 and 13.8 mo, respectively [78–81]. Neither of the two combinations proved superior over the other, but equivalence was not tested, with response rates of 46% and 49% for M-VAC and GC, respectively. The long-term survival results confirmed the anticipated equivalence of the two regimens. The major difference between the above-mentioned combinations was toxicity, with GC being less toxic. With cisplatin-containing combination chemotherapy, patients with lymph node metastases only, good PS, and an adequate renal function may achieve excellent response rates, including a high degree of complete responses, with up to 20% of patients achieving long-term disease-free survival (LE: 1b) [33,78,82,83]. Carboplatin combination chemotherapy is less effective than cisplatin-based chemotherapy in terms of complete response (CR) and survival (LE: 2a).

Other nonplatinum combination chemotherapy has produced substantial responses in first- and second-line use but has not been tested against standard chemotherapy in fit patients or in a purely unfit patient group (LE: 2a). Small-sized phase 2 trials provide evidence of moderate response rates for single agents or nonplatinum combinations at second-line use (LE: 2a). Postchemotherapy surgery after a partial or complete response may contribute to long-term disease-free survival (LE: 3). PS and the presence or absence of visceral metastases are independent prognostic factors for survival. These factors are at least as important as the type of chemotherapy administered (LE: 3).

Overall indication and selection for treatment is guided by prognostic factors (grade of recommendation: B). The first-line treatment for patients fit enough to sustain cisplatin is cisplatin-containing combination chemotherapy with GC, M-VAC (preferably with granulocyte colony-stimulating factor [GCSF]), or high-dose M-VAC with GCSF (grade of recommendation: A). Carboplatin and nonplatinum combination chemotherapy as first-line treatment in patients fit for cisplatin is not recommended (grade of recommendation: B) unless patients are unfit for cisplatin (grade of recommendation: C). At present, there are, as yet, insufficient data to provide a recommendation on standard second-line chemotherapy. Therefore, second-line therapy should be provided within a clinical trial setting. Single agents or paclitaxel/gemcitabine, if the patient has a good PS, may be considered (grade of recommendation: C).

7. Follow-up of patients with muscle-invasive bladder cancer

The authors would like to stress that any advice related to follow-up is entirely based on expert consensus and level-4 evidence data. An appropriate schedule for disease monitoring should be based on the natural timing of recurrence, the probability of disease recurrence, functional deterioration at particular sites, and consideration of treatment of a recurrence [84]. In general, follow-up oncologic surveillance can be stopped after 5 yr, but continuation with functional surveillance according to type of urinary diversion and general status is recommended. For suggestions and recommendations regarding general follow-up in various tumour stages and situations, refer to Tables 4 and 5.

The prognosis of patients with a pelvic recurrence depends on the type of recurrence. Systemic chemotherapy, local surgery, or RT can sometimes provide a prolonged survival or provide significant palliation of symptoms in most cases.

Distant recurrences are seen in up to 50% of patients treated with cystectomy. Most recurrences occur in the first 24 mo, although progression has been observed after >10 yr. Pathologic stage of the primary tumour and nodal status are risk factors. The most likely sites for distant recurrences are the lungs, liver, and bones [85]. Upper urinary tract recurrence is rarely seen (2–7%), but when it develops, it usually does so within 22–40 mo after cystectomy [56,84,85]. Surveillance regimens often fail to detect tumours before symptoms develop. However, radical nephroureterectomy can provide prolonged survival [86].

The incidence of secondary urethral tumour is 5–17% and is particularly likely to occur at 1–3 yr after surgery. Prophylactic urethrectomy at the time of cystectomy is no longer justified in most patients.

Table 4 – Conclusions and recommendations for follow-up of muscle-invasive bladder cancer according to specific condition

Condition	Conclusion or recommendation	LE or grade of recommendation
Secondary urethral tumour	Staging and treatment should be performed as for primary urethral tumour.	3
	For noninvasive tumour, local organ conservative treatment is advised.	C
	In isolated invasive disease, a urethrectomy should be performed.	B
	Urethral washes and cytology are not recommended as standard follow-up.	A
Pelvic recurrence	The prognosis is poor.	2b
	Treatment should be individualized depending on the local extent and symptoms.	
	RT, chemotherapy, and possibly surgery are options for treatment—either alone or in combination.	C
Upper urinary tract recurrence	Specific upper urinary tract imaging is only indicated in case of clinical symptoms; radical nephroureterectomy can provide prolonged survival.	B

LE = level of evidence; RT = radiotherapy.

Table 5 – Suggestions for general follow-up based on the stage of initial tumour after cystectomy

	Mo after cystectomy								
	3	6	12	18	24	30	36	48	60
<pT1									
Ultrasound kidneys	×	–	–	–	–	–	–	–	–
CT/MRI thor/abd plus UUT*	–	–	×	–	×	–	×	×	×
Lab**, sed, culture, and cytology	×	×	×	–	×	–	×	×	×
pT2									
Ultrasound kidneys	×	–	–	–	–	–	–	–	–
CT/MRI thor/abd, plus UUT*	–	×	×	×	×	–	×	×	×
Lab, sed, culture, and cytology	×	×	×	–	×	–	×	×	×
>PT3 of N+									
Ultrasound kidneys	×	–	–	–	–	–	–	–	–
CT/MRI thor/abd, plus UUT*	×	×	×	×	×	×	×	×	×
Lab, sed, culture, and cytology	×	×	×	–	×	×	×	×	×

abd = abdominal; CT = computed tomography; MRI = magnetic resonance imaging; lab = laboratory investigations; sed = urine sediment analysis; thor = thoracic; UUT = upper urinary tract.
* Retrograde uretero-pyelography and sampling should be performed.
** Blood chemistry, including serum creatinine, or renal function and blood gas analysis.

In men, the most important risk factor for the development of urethral recurrence is prostatic stromal invasion (21–64%) [87,88]. In women, the risk factor is disease at the bladder neck [89]. Multiple studies demonstrate that the risk of urethral recurrence after orthotopic diversion (0.9–4%) [87,90,91] is significantly less than after non-orthotopic diversion (6.4–11.1%). Routine urethral washes and urine cytology do not appear to have any effect on survival [92,93].

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Study concept and design: Stenzl.
Acquisition of data: Stenzl, Cowan, Ribal, Jakse, Kuczyk, Merseburger, De Santis, Sherif, Witjes.
Analysis and interpretation of data: Stenzl, Cowan, Ribal, Jakse, Kuczyk, Merseburger, De Santis, Sherif, Witjes.
Drafting of the manuscript: Stenzl.
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References

[1] Oosterlinck W, Lobel B, Jakse G, Malmström P-U, Stöckle M, Sternberg C, The EAU Working Group on Oncological Urology. Guidelines on bladder cancer. Eur Urol 2002; 41:105–12.

[2] Centre for Evidence-Based Medicine. Levels of evidence. http://www.cebm.net/index.aspx?o=1025. Accessed October 24, 2008.

[3] Ferlay J, Autier P, Boniol M, Heanue M, Colombet M, Boyle P. Estimates of the cancer incidence and mortality in Europe in 2006. Ann Oncol 2007;18:581–92.

[4] Kogevinas M, Mannetje A, Cordier S, et al. Occupation and bladder cancer among men in Western Europe. Cancer Causes Control 2003;14:907–14.

[5] Chrouser K, Leibovich B, Bergstralh E, Zincke H, Blute M. Bladder cancer risk following primary and adjuvant external beam radiation for prostate cancer. J Urol 2005;174:107–10, discussion 110–1.

[6] Boorjian S, Cowan JE, Konety BR, et al. Bladder cancer incidence and risk factors in men with prostate cancer: results from Cancer of the Prostate Strategic Urologic Research Endeavor. J Urol 2007;177:883–7, discussion 887–8.

[7] Vaidya A, Soloway MS, Hawke C, Tiguert R, Civantos F. De novo muscle invasive bladder cancer: is there a change in trend? J Urol 2001;165:47–50, discussion 50.

[8] McGrath M, Michaud DS, De Vivo I. Hormonal and reproductive factors and the risk of bladder cancer in women. Am J Epidemiol 2006;163:236–44.

[9] Sobin DH, Wittekind Ch, eds. TNM Classification of Malignant Tumours. 6th ed. New York, NY: Wiley-Liss; 2002. p. 199–202.

[10] Sauter G, Algaba F, Amin M, et al. Tumours of the urinary system: non-invasive urothelial neoplasias. In: Eble JN, Sauter G, Epstein Jl, Sesterhenn I, editors. World Health Organization Classification of Tumors: Pathology and Genetics of the Urinary System and Male Genital Organs. Lyon, France: IARCC Press; 2004. p. 29–34.

[11] Jimenez RE, Gheiler E, Oskanian P, et al. Grading the invasive component of urothelial carcinoma of the bladder and its relationship with progression-free survival. Am J Surg Pathol 2000;24:980–7.

[12] Fossa SD, Ous S, Berner A. Clinical significance of the ''palpable mass'' in patients with muscle-infiltrating bladder cancer undergoing cystectomy after preoperative radiotherapy. Br J Urol 1991;67:54–60.

[13] Paik ML, Scolieri MJ, Brown SL, Resnick MI. Limitations of computed tomography in the preoperative staging of upper tract urothelial carcinoma. Urology 2000;56:930–4.

[14] Van Der Molen AJ, Cowan NC, Mueller-Lisse UG, Nolte-Ernsting CC, Takahashi S, Cohan RH. CT urography: definition, indications and techniques. A guideline for clinical practice. Eur Radiol 2008;18:4–17.

[15] Holmang S, Hedelin H, Anderstrom C, Holmberg E, Johansson SL. Long-term follow-up of a bladder carcinoma cohort: routine follow-up urography is not necessary. J Urol 1998;160:45–8.

[16] Palou J, Rodriguez-Rubio F, Huguet J, et al. Multivariate analysis of clinical parameters of synchronous primary superficial bladder cancer and upper urinary tract tumor. J Urol 2005;174:859–61, discussion 861.

[17] Nolte-Ernsting C, Cowan N. Understanding multislice CT urography techniques: many roads lead to Rome. Eur Radiol 2006;16:2670–86.

[18] Raitanen M-P, Aine R, Rintala E, et al. Differences between local and review urinary cytology in diagnosis of bladder cancer. An interobserver multicenter analysis. Eur Urol 2002;41:284–9.

[19] Lokeshwar VB, Habuchi T, Grossman HB, et al. Bladder tumor markers beyond cytology: International Consensus Panel on bladder tumor markers. Urology 2005;66 (Suppl 1):35–63.

[20] Babjuk M, Oosterlinck W, Sylvester R, Kaasinen E, Böhle A, Palou-Redorta J. EAU guidelines on non-muscle-invasive urothelial carcinoma of the bladder. Eur Urol 2008;54: 303–14.

[21] Stenzl A, Colleselli K, Bartsch G. Update of urethra-sparing approaches in cystectomy in women. World J Urol 1997;15:134–8.

[22] Heidenreich A, Aus G, Bolla M, et al. EAU guidelines on prostate cancer. Eur Urol 2008;53:68–80.

[23] Damiano R, Di Lorenzo G, Cantiello F, et al. Clinicopathologic features of prostate adenocarcinoma incidentally discovered at the time of radical cystectomy: an evidence-based analysis. Eur Urol 2007;52:648–57.

[24] Mallampati GK, Siegelman ES. MR imaging of the bladder. Magn Reson Imaging Clin N Am 2004;12:545–55, vii.

[25] Kim JK, Park SY, Ahn HJ, Kim CS, Cho KS. Bladder cancer: analysis of multi-detector row helical CT enhancement pattern and accuracy in tumor detection and perivesical staging. Radiology 2004;231:725–31.

[26] Kundra V, Silverman PM. Imaging in oncology from the University of Texas M.D. Anderson Cancer Center. Imaging in the diagnosis, staging, and follow-up of cancer of the urinary bladder. AJR Am J Roentgenol 2003;180:1045–54.

[27] Jager GJ, Barentsz JO, Oosterhof GO, Witjes JA, Ruijs SJ. Pelvic adenopathy in prostatic and urinary bladder carcinoma: MR imaging with a three-dimensional TI-weighted magnetization-prepared-rapid gradient-echo sequence. AJR Am J Roentgenol 1996;167:1503–7.

[28] Barentsz JO, Engelbrecht MR, Witjes JA, de la Rosette JJ, van der Graaf M. MR imaging of the male pelvis. Eur Radiol 1999;9:1722–36.

[29] Cowan NC, Turney BW, Taylor NJ, McCarthy CL, Crew JP. Multidetector computed tomography urography for diagnosing upper urinary tract urothelial tumour. BJU Int 2007;99:1363–70.

[30] Dorfman RE, Alpern MB, Gross BH, Sandler MA. Upper abdominal lymph nodes: criteria for normal size determined with CT. Radiology 1991;180:319–22.

[31] Lauenstein TC, Goehde SC, Herborn CU, et al. Whole-body MR imaging: evaluation of patients for metastases. Radiology 2004;233:139–48.

[32] Schmidt GP, Schoenberg SO, Reiser MF, Baur-Melnyk A. Whole-body MR imaging of bone marrow. Eur J Radiol 2005;55:33–40.

[33] 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.
[34] Sanchez-Ortiz RF, Huang WC, Mick R, Van Arsdalen KN, Wein AJ, Malkowicz SB. 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.
[35] Stein JP. Contemporary concepts of radical cystectomy and the treatment of bladder cancer. J Urol 2003;169:116–7.
[36] 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.
[37] Vale CA, 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.
[38] Neoadjuvant cisplatin, methotrexate, and vinblastine chemotherapy for muscle-invasive bladder cancer: a randomised controlled trial. International collaboration of trialists. Lancet 1999; 354:533–40.
[39] 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.
[40] Sternberg CN, de Mulder PH, Schornagel JH, et al., European Organization for Research, 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.
[41] 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.
[42] Hautmann RE, Abol-Enein H, Hafez K, et al. Urinary diversion. Urology 2007;69(Suppl):17–49.
[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] Miller DC, Taub DA, Dunn RL, Montie JE, Wei JT. The impact of comorbid disease on cancer control and survival following radical cystectomy. J Urol 2003;169: 105–9.
[45] Hautmann RE, Paiss T. Does the option of the ileal neobladder stimulate patient and physician decision toward earlier cystectomy? J Urol 1998;159:1845–50.
[46] Stenzl A, Nagele U, Kuczyk M, et al. Cystectomy: technical considerations in male and female patients. EAU Update Series 2005;3:138–46.
[47] Vallancien G, Abou El Fettouh H, Cathelineau X, Baumert H, Fromont G, Guillonneau B. Cystectomy with prostate sparing for bladder cancer in 100 patients: 10-year experience. J Urol 2002;168:2413–7.
[48] Muto G, Bardari F, D'Urso L, Giona C. Seminal sparing cystectomy and ileocapsuloplasty: long-term follow-up results. J Urol 2004;172:76–80.
[49] 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.
[50] 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.
[51] 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.
[52] 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.
[53] 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.
[54] 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.
[55] Ghoneim MA, Abol-Enein H. Lymphadenectomy with cystectomy: is it necessary and what is its extent? Eur Urol 2004;46:457–61.
[56] Fleischmann A, Thalmann GN, Markwalder R, Studer UE. Extracapsular extension of pelvic lymph node metastases from urothelial carcinoma of the bladder is an independent prognostic factor. J Clin Oncol 2005; 23:2358–65.
[57] 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.
[58] Stenzl A. Bladder substitution. Curr Opin Urol 1999;9: 241–5.
[59] Tanrikut C, McDougal WS. Acid-base and electrolyte disorders after urinary diversion. World J Urol 2004;22:168–71.
[60] Farnham SB, Cookson MS. Surgical complications of urinary diversion. World J Urol 2004;22:157–67.
[61] 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.
[62] 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.
[63] 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.
[64] Figueroa AJ, Stein JP, Dickinson M, et al. Radical cystectomy for elderly patients with bladder carcinoma: an

updated experience with 404 patients. Cancer 1998;83: 141–7.
[65] 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.
[66] Ubrig B, Lazica M, Waldner M, Roth S. Extraperitoneal bilateral cutaneous ureterostomy with midline stoma for palliation of pelvic cancer. Urology 2004;63:973–5.
[67] Rodel C, Grabenbauer GG, Kuhn R, et al. Combined-modality treatment and selective organ preservation in invasive bladder cancer: long-term results. J Clin Oncol 2002;20:3061–71.
[68] Zietman AL, Grocela J, Zehr E, et al. Selective bladder conservation using transurethral resection, chemotherapy, and radiation: management and consequences of Ta, T1, and Tis recurrence within the retained bladder. Urology 2001;58:380–5.
[69] Shipley WU, Kaufman DS, Zehr E, et al. Selective bladder preservation by combined modality protocol treatment: long-term outcomes of 190 patients with invasive bladder cancer. Urology 2002;60:62–7, discussion 67–8.
[70] Herr HW. Transurethral resection of muscle-invasive bladder cancer: 10-year outcome. J Clin Oncol 2001;19: 89–93.
[71] Sternberg CN. Perioperative chemotherapy in muscle-invasive bladder cancer to enhance survival and/or as a strategy for bladder preservation. Semin Oncol 2007;34:122–8.
[72] Freiha F, Reese J, Torti FM. A randomized trial of radical cystectomy versus radical cystectomy plus cisplatin, vinblastine and methotrexate chemotherapy for muscle invasive bladder cancer. J Urol 1996;155:495–9, discussion 499–500.
[73] Stockle M, Meyenburg W, Wellek S, et al. Adjuvant polychemotherapy of nonorgan-confined bladder cancer after radical cystectomy revisited: long-term results of a controlled prospective study and further clinical experience. J Urol 1995;153:47–52.
[74] Studer UE, Bacchi M, Biedermann C, et al. Adjuvant cisplatin chemotherapy following cystectomy for bladder cancer: results of a prospective randomized trial. J Urol 1994;152:81–4.
[75] Skinner DG, Daniels JR, Russell CA, et al. Adjuvant chemotherapy following cystectomy benefits patients with deeply invasive bladder cancer. Semin Urol 1990;8: 279–84.
[76] Sylvester R, Sternberg C. The role of adjuvant combination chemotherapy after cystectomy in locally advanced bladder cancer: what we do not know and why. Ann Oncol 2000;11:851–6.
[77] 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.
[78] 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.
[79] 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.
[80] Logothetis CJ, Dexeus FH, Finn L, et al. A prospective randomized trial comparing MVAC and CISCA chemotherapy for patients with metastatic urothelial tumors. J Clin Oncol 1990;8:1050–5.
[81] Sternberg CN, de Mulder P, Schornagel JH, et al., EORTC Genito-Urinary Cancer Group. 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.
[82] Stadler WM, Hayden A, von der Maase H, et al. Long-term survival in phase II trials of gemcitabine plus cisplatin for advanced transitional cell cancer. Urol Oncol 2002;7:153–7.
[83] Hussain M, Vaishampayan U, Du W, Redman B, Smith DC. Combination paclitaxel, carboplatin, and gemcitabine is an active treatment for advanced urothelial cancer. J Clin Oncol 2001;19:2527–33.
[84] Malkowicz SB, van Poppel H, Mickisch G, et al. Muscle-invasive urothelial carcinoma of the bladder. Urology 2007;69(Suppl 1):3–16.
[85] Bochner BH, Montie JE, Lee CT. Follow-up strategies and management of recurrence in urologic oncology bladder cancer: invasive bladder cancer. Urol Clin North Am 2003;30:777–89.
[86] Sanderson KM, Cai J, Miranda G, Skinner DG, Stein JP. Upper tract urothelial recurrence following radical cystectomy for transitional cell carcinoma of the bladder: an analysis of 1,069 patients with 10-year follow-up. J Urol 2007;177:2088–94.
[87] Freeman JA, Tarter TA, Esrig D, et al. Urethral recurrence in patients with orthotopic ileal neobladders. J Urol 1996;156:1615–9.
[88] Levinson AK, Johnson DE, Wishnow KI. Indications for urethrectomy in an era of continent urinary diversion. J Urol 1990;144:73–5.
[89] Stenzl A, Draxl H, Posch B, Colleselli K, Falk M, Bartsch G. The risk of urethral tumors in female bladder cancer: can the urethra be used for orthotopic reconstruction of the lower urinary tract? J Urol 1995;153:950–5.
[90] Nieder AM, Sved PD, Gomez P, Kim SS, Manoharan M, Soloway MS. Urethral recurrence after cystoprostatectomy: implications for urinary diversion and monitoring. Urology 2004;64:950–4.
[91] Varol C, Thalmann GN, Burkhard FC, Studer UE. Treatment of urethral recurrence following radical cystectomy and ileal bladder substitution. J Urol 2004;172:937–42.
[92] Clark PE, Stein JP, Groshen SG, et al. The management of urethral transitional cell carcinoma after radical cystectomy for invasive bladder cancer. J Urol 2004;172:1342–7.
[93] Lin DW, Herr HW, Dalbagni G. Value of urethral wash cytology in the retained male urethra after radical cystoprostatectomy. J Urol 2003;169:961–3.