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Original – Bladder cancer

Update of the Clinical Guidelines of the European Association of Urology on muscle-invasive and metastatic bladder carcinoma*

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A B S T R A C T

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 cystectomy. An orthotopic bladder substitute should be offered to both male and female patients

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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: a) natural timing of recurrence; b) probability of disease recurrence; c) functional deterioration at particular sites; and d) 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 EAUguidelines 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.

Actualización de las Guías Clínicas de la Asociación Europea de Urología sobre el carcinoma vesical músculo-invasivo y metastásico

RESUMEN

Contexto: La aparición de nuevos datos relacionados con el diagnóstico y tratamiento de cáncer vesical músculo-invasivo y metastásico (CaV-MiM) ha obligado a una actualización de las Guías sobre el CaV-MiM de la Asociación Europea de Urología (EAU).

Objetivo: Revisión de las nuevas guías de la EAU para el CAV-MiM.

Evidencia adquirida: Un grupo de urólogos, oncólogos y radiólogos designados por el Comité de Guías Clínicas de la EAU ha realizado un exhaustivo trabajo de revisión de la literatura procedente de Medline, el registro central Cochrane de revisiones sistemáticas y las citas bibliográficas de publicaciones y artículos de revisión. Se han tenido en cuenta las recomendaciones basadas en la literatura previa disponible sobre este aspecto. Además, han sido añadidos niveles de evidencia y grados de recomendación, según las modificaciones del *Oxford Centre for Evidence-based Medicine*.

Evidencia sintetizada: El diagnóstico de cáncer vesical músculo-invasivo (CaVMI) se realiza mediante la resección transuretral y el consiguiente estudio histopatológico. Una vez confirmada la existencia de CaVMI es preciso realizar el estadiaje mediante tomografía computarizada toraco-abdómino-pélvica, si se dispone de ella. Actualmente, la quimioterapia adyuvante solamente se recomienda en el contexto de ensayos clínicos. La cistectomía radical es el tratamiento de elección en ambos sexos, y la linfadenectomía debe constituir una parte integral de la misma. Tanto a hombres como a mujeres se les debe ofrecer la sustitución vesical ortotópica siempre que no existan contraindicaciones, tales como la existencia de tumor en el margen uretral. En la actualidad, los tratamientos multimodales para la conservación vesical en casos de enfermedad localizada constituyen una alternativa terapéutica solamente en pacientes seleccionados, adecuadamente informados, y en aquellos en los que se desestima la cistectomía por motivos clínicos o personales. Los protocolos de seguimiento deben diseñarse sobre la base de: a) historia natural de la recurrencia; b) probabilidades de recurrencia; c) deterioro funcional en localizaciones específicas; y d) consideraciones sobre el tratamiento de la recurrencia. En la enfermedad metastásica el tratamiento de primera línea para los pacientes con un estado general adecuado para tolerar el cisplatino es la quimioterapia combinada basada en este fármaco. Actualmente no existe una quimioterapia estandarizada de segunda línea.

Conclusiones: Estas guías de la EAU constituyen un resumen de la exhaustiva visión de conjunto de las guías recientemente actualizadas del CaV-MiM, publicadas en las guías clínicas de la EAU, también disponibles en la *National Guideline Clearinghouse*.

Palabras clave:
Cáncer vesical músculo-invasivo
Quimioterapia
Cistectomia
Derivación urinaria
Guías clínicas

Introduction

Most publications regarding muscle-invasive and metastatic bladder cancer (MiM-BC) are based on retrospective studies, including some large multicenter studies and other well-designed controlled studies. There are few randomized studies on the diagnosis and surgical treatment of MiM-BC, and qualified, evidence-based data on relevant clinical aspects do not reach the levels obtained in some of the medical specialties.

Methods

The recommendations described in current clinical guidelines are based on an extensive literature search performed through Medline, the Cochrane Central Register of Systematic Reviews, and reference lists in publications and review articles. The recommendations based on previous literature on this subject were taken into account[1]. The latest update on MiM-BC was performed using the references found in Medline and other public databases. Based on the results obtained from this search, all members of the committee established the conclusions and recommendations on each of the subjects relating to MiM-BC. Levels of evidence and grades of recommendation are established according to the Oxford Centre for Evidence-based Medicine Levels of Evidence[2]. The purpose of grades of recommendation is to provide transparency between the underlying evidence and the recommendation offered. Finally, the most significant conclusions are summarized, paying greater attention to changes made with regard to previous versions of the guidelines, with the corresponding levels of evidence (LE: 1-4; Table 1) and grades of recommendation (A-C; Table 1).

Epidemiology and risk factors

In 2006, the estimated number of patients diagnosed with bladder cancer (BC) in Europe was 104,000 (82,800 men and 21,600 women), accounting for 6.6% of all cancers diagnosed in men and 2.1% in women. The male-to-female ratio was 3.8:1. BC was fourth leading cancer in men. BC causes 4.1% of all deaths from cancer in men and 1.8% of deaths in women[3]. Smoking is the main risk factor clearly related to BC, present in approximately 50-65% of cases in men and 20-30% of cases in women. Occupational exposure is considered the second most important risk factor. According to different series, 20-25% of all cases of BC are work-related, with a downward trend in recent series[4]. There have been reports of an increased rate of bladder cancer secondary to external beam radiation therapy (EBRT) used in gynecological malignancies, with a relative risk of 2 to 4[5]; in prostate cancer (CaP) patients, the incidence of BC was significantly lower in patients treated with radical prostatectomy (RP) than in patients undergoing EBRT[6]. Sex-related differences in BC prevalence appear be due to reasons other than smoking or chemical exposure[7,8].

Distribution by grade and stage

The 2002 TNM classification, approved by the International Union Against Cancer (UICC), is widely accepted and the basis for the current guidelines[9]. Use of the 2004 World Health Organization (WHO) classification is advised, because it should lead to a more consistent diagnosis of tumors[10]. However, until the 2004 WHO classification has been validated by new clinical trials, tumor grade should be established using both WHO classifications (1973 and 2004). Most clinical trials published so far have used the 1973 WHO classification. Therefore, these guidelines are based on this classification.

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

Level	Type of evidence
1a	Evidence obtained from meta-analysis of randomized trials
1b	Evidence obtained from at least one randomized trial
2a	Evidence obtained from at least one well-designed controlled prospective study without randomization
2b	Evidence obtained from at least one well designed quasi-experimental study
3	Evidence obtained from well-designed non-experimental descriptive studies, such as comparative studies, correlation studies or case-control studies
4	Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities
Grade	**Nature of recommendation**
A	Based on clinical trials of good quality and consistency addressing the specific recommendations and including at least one randomized clinical trial
B	Based on well-designed clinical trials, but without randomized trials
C	Made despite the absence of directly applicable clinical studies of good quality

Table 2 – Recommendations on bladder tumor staging

Diagnosis of muscle-invasive BC
Cystoscopy and biopsy Imaging only when staging causes discrepancies in the selection of the treatment options
Local staging for patients eligible for radical cystectomy (grade of recommendation: B)
MRI with fast dynamic contrast enhancement MDCT with contrast enhancement
For patients with confirmed muscle-invasive BC (grade of recommendation: B)
MDCT of the chest, abdomen and pelvis, including MDCTU for complete examination of the upper urinary tract Lesser alternatives (if MDCT is not available) are intravenous urography and plain chest X-ray (grade of recommendation: B)

BC: bladder cancer; MRI: magnetic resonance imaging; MDCT: Multidetector-row computed tomography (helical); MDCTU: multidetector-row computed tomography urography (helical).

Diagnostic procedures

Bimanual examination must be performed before and after transurethral resection (TUR) to evaluate whether there is a palpable mass and if the tumor is adhered to the pelvic wall[11,12]. When an invasive BC is suspected on cystoscopic examination, appropriate imaging studies should be performed prior to TUR. After TUR, it is impossible to differentiate the inflammatory reaction of perivesical fat from tumor growth[13]. Multidetector-row computed tomography urography (MDCTU) is the preferred imaging test for diagnosis and staging of bladder and upper urinary tract cancer (Table 2). This procedure may be considered an alternative to intravenous urography (IVU)[14] in invasive tumors of the upper urinary tract because it provides more complete information (LE: 4), but has the drawback of greater radiation exposure than conventional IVU. IVU allows large bladder tumors to be detected as filling defects or deformities of the bladder wall. IVU also provides information on the presence of a ureteral tumor occurring as a filling defect or the presence of hydronephrosis. The need for an IVU is currently questioned in patients diagnosed of bladder tumor due to the low incidence of significant findings with this examination[14,15] (LE: 3). The incidence of upper urinary tract tumors is low (1.8%), but may be up to 7.5% in the case of tumors located in the trigone[16]. Transabdominal ultrasound permits characterization of large renal masses, detection of hydronephrosis and visualization of intravesical filling defects. Combined with plain abdominal X-ray, it can be as accurate as IVU for diagnosing the cause of hematuria[17] (LE: 3). Examination by urinary cytology and urine markers yielded a sensitivity and specificity higher than 90% in high-grade tumors or carcinoma in situ[18,19] (LE: 2b). It is particularly useful in MiM-BC, because most of these tumors are high grade. This is also applicable to the urinary markers, although no urinary marker has been registered as a specific marker for the diagnosis of invasive BC. Definitive diagnosis of BC depends on endoscopic examination of the bladder and histological evaluation of the resected tissue. In general, cystoscopy is performed on an outpatient basis, using flexible or rigid instruments. If a bladder tumor is visualized by careful ultrasonography, multidetector computed tomography (CT), or magnetic resonance imaging (MRI), cystoscopy can be omitted because the patient will undergo TUR for histological diagnosis.

Transurethral resection of invasive bladder tumors

The goal of any TUR or repeat TUR in invasive bladder tumors is to obtain a firm diagnosis, which means including bladder muscle in the resected fragments. Further information can be obtained in the recently published non-muscle-invasive BC guidelines[20].

Bladder and prostatic urethral biopsies

Involvement of the prostatic urethra and ducts in men with bladder tumors is usually more common when the tumor is located on the trigone or bladder neck, in the presence of diffuse bladder CIS, and in multifocal tumors[19,20] (LE: 3). In these cases and/or when abnormalities are seen in the prostatic urethra, biopsies taken using resection loop from the precolicular urethra are recommended (grade of recommendation C). Special care must be taken in women with tumors at the trigone and bladder neck, when the possibility of urethral preservation is considered for subsequent orthotopic bladder substitution. Bladder neck biopsies in women

are advisable but not mandatory, as they allow for fresh section analysis of the urethral margin at the time of bladder substitution surgery[21] (LE: 4).

Concomitant prostate cancer

Investigations for prostate cancer should be performed according to the EAU guidelines on CaP[22].

Staging

Imaging techniques

Local staging of invasive bladder cancer

Both CT and MRI can be used to assess the level of local[23] invasion, but they are unable to detect microscopic invasion of perivesical fat (T3a). Therefore, the aim of CT and MRI is to detect T3b stage disease or higher. In the bladder, MRI achieves better soft tissue resolution compared with CT, but has poorer spatial resolution. In the time before the availability of multidetector-row computed tomography (MDCT), MRI provided higher accuracy for local staging. The accuracy of MRI for primary tumor staging ranges from 73-96% (mean 85%). These values are 10-33% (mean 19%) higher than those obtained with CT.

Fast dynamic contrast-enhanced MRI helps to differentiate bladder tumor from surrounding tissues because enhancement of the tumor occurs earlier than the normal bladder wall due to tumor neovascularisation[13]. This modality of MRI acquires images at a rate of one image per second, so it is very useful for differentiating the tumor from postbiopsy tissue reaction[13]. The advantages of CT include faster examination, wider coverage in a single breath hold, and lower susceptibility to some individual patient factors. The accuracy of CT in determining extravesical tumor extension ranges from 55% to 92%[24], and increases with more advanced disease[25]. The accuracy of MDCT for detection and staging of the BC showed that CT had lower sensitivity (89% versus 100%) and higher specificity (95% versus 73%) compared to MRI for diagnosis of perivesical invasion, while the cancer detection rate and overall accuracy for perivesical invasion were similar[26].

Imaging techniques for lymph node involvement and metastasis

The assessment of lymph node involvement based only on size is limited by the inability of CT and MRI to identify metastasis in normal sized or minimally enlarged nodes. Sensitivies for detection of lymph node metastases are low, ranging from 48% and 87%. Specificities are also low, reaching 64%, although lymph node involvement may be due to benign disease. Overall, the results obtained by CT and MRI in detecting lymph node metastases are similar for various primary pelvic tumors[27,28]. Pelvic lymph nodes > 8 mm and abdominal nodes > 10 mm in diameter in maximum short axis diameter (MSAD) should be considered as enlarged nodes on CT and MRI[14,28-31].

Before any treatment with curative intent, it is essential to rule out the presence of distant metastasis. MDCT and MRI are the diagnostic techniques of choice to detect lung and liver metastases (LE: 2b-3).

Bone and brain metastases are rare in invasive BC. Therefore, bone scan and brain imaging are not indicated, except when the patient has symptoms or specific signs suggesting the presence of metastasis in these locations[14,29].

MRI is more sensitive and specific for diagnosing bone disease than bone scintigraphy[31,32] (LE: 2b).

Localized muscle-invasive bladder cancer

Neoadjuvant chemotherapy

The advantages of neoadjuvant chemotherapy (administered to patients with operable transitional cell carcinoma of the bladder before the planned surgery or radiation therapy) are numerous: chemotherapy is delivered in an earlier stage, when the burden of micrometastic disease is probably lower; in vivo chemosensitivity can be tested, and better tolerance of chemotherapy is expected before performing cystectomy. However, there are also some substantial disadvantages to neoadjuvant chemotherapy. Staging errors may result in overtreatment, delayed cystectomy may compromise the outcome of patients resistant to chemotherapy[33-35], and the side effects of chemotherapy may alter the outcome of cystectomy and urinary diversion[36]. In recently published studies and meta-analyses neoadjuvant chemotherapy improved overall survival (OS) by 5-8%, so neoadjuvant cisplatin-containing combination chemotherapy should be considered as an option for muscle-invasive BC, irrespective of definitive treatment (grade of recommendation: A)[37-40].

Neoadjuvant chemotherapy is not recommended in patients with performance status (PS) = 2 and impaired renal function (grade of recommendation: B). Chemotherapy as single therapy is not recommended as primary treatment of localized BC (grade of recommendation: A)[41].

Radical surgery and urinary diversion

Radical cystectomy (RC) is the standard treatment for localized muscle-invasive BC in most Western countries[42,43].

Interest in quality of life (QoL) issues has promoted the trend toward urethral preservation to perform an orthotopic neobladder, as well as for intrapelvic autonomic nerve sparing to improve potency and continence, and for bladder preservation treatment modalities such as radiotherapy (RT) and/or chemotherapy. Patient age and PS influence the choice of primary tumor therapy, as well as the type of urinary diversion[44]. Delay in performing cystectomy (conventionally considered the treatment after 90 days of diagnosis) affects both the outcome of disease and the type of urinary diversion[33,45].

The recommendations for cystectomy and urinary diversion are shown in Table 3.

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

RC in T2–T4a, N0–NX, M0, and high-risk non-muscle-invasive BC as described above (grade of recommendation: B)
There is no preoperative indication of RT (grade of recommendation: A)
Lymph node dissection should be an integral part of cystectomy. Extent has not been established (grade of recommendation: B)
Urethral preservation is reasonable if margins are negative; if no bladder substitution is done, urethra should be checked regularly (grade of recommendation: B)
Orthotopic bladder substitution should be offered to both male and female patients in the absence of contraindications and when there is no tumor in the urethra or urethral margin (grade of recommendation: B)
Laparoscopic and robot-assisted cystectomy may be an option; current data, however, do not provide sufficient information on its advantages and disadvantages (grade of recommendation: C)
Treatment is recommended in centers experienced in complex diversion techniques and postoperative management (grade of recommendation: B)
Before cystectomy, the patient should be adequately informed about all possible alternatives, and the final decision you should be agreed between the patient and the surgeon (grade of recommendation: B)

BC: bladder cancer; RC: radical cystectomy; RT: radiotherapy.

Surgical technique and extent

RC involves the removal of the bladder and adjacent organs, including the prostate and seminal vesicles in men and the uterus and adnexa in women[46], in addition to the corresponding lymph nodes. However, complete removal of the prostate in men and vaginal resection in women has recently been questioned[47,48]. Various techniques of partial prostate-sparing cystoprostatectomy have been proposed in men with localized cancer, and the results of a series with a long follow-up period have been published. Autopsy studies as well as studies aimed at detecting the presence of CaP in cystoprostatectomy specimens suggest that in approximately 23-54% of patients a CaP is found in patients undergoing this technique. Up to 29% of these cases may be clinically significant, locally recurrent or even metastatic cancer[49-51]. Overall, in some series, no CaP or urothelial prostate carcinoma is found in only 26-33% of patients undergoing cystoprostatectomy.

In retrospective studies extended lymphadenectomy has been reported to improve survival in patients with muscle-invasive BC. However, the therapeutic value of extended lymph node dissection is still unknown and a standardized lymph node dissection has yet to be established[52-54]. There are retrospective and prospective studies[55,56] with regard to the anatomical zones that should be included in lymphadenectomy, showing that lymph nodes in BC patients are not found outside the pelvis if the pelvic lymph nodes are free of tumor. Furthermore, both OS and progression free survival could be correlated with the amount of lymph nodes removed during surgery[53,56].

A distal ureteral segment should be resected (unspecified length) and in case of CIS a fresh section for evaluation of the ureteral surgical margin should be performed[46,57]. Urethrectomy is recommended (in both sexes) if there is a positive margin in the urethral dissection, or if the primary tumor is located in the bladder neck or the urethra (in women), or if the tumor extensively infiltrates the prostate[41,43,57].

Urinary diversion after radical cystectomy

From an anatomical standpoint three possible forms of diversion are considered: abdominal, urethral, and rectosigmoid. Different segments of the intestinal tract have been used for reconstruction of the urinary tract, including the stomach, ileum, colon, and appendix[58]. Although various studies have compared QoL related aspects, such as sexual function, urinary continence and body image in patients groups with different types of urinary diversion, further studies are needed in this field with regard to preoperative tumor staging and functional status of the patient, socioeconomic status, time interval to primary surgery, and some other aspects.

Eligible patients for any type of urinary diversion have to be motivated to learn and sufficiently skillful to manage their diversion. Debilitating neurological or psychiatric diseases, a short life expectancy, impaired liver or renal function and the presence of transitional carcinoma in the urethral margin or another surgical margin are contraindications to the more complex forms of urinary diversion. Specific contraindications for an orthotopic neobladder are: high doses of preoperative RT, complex urethral strictures and severe urethral sphincter-related incontinence[59-61].

Oncological outcomes of surgery

According to the literature, recurrence-free and overall survival in men and women was 66-68% and 58-66% respectively at 5 years, and 60-73% and 43-49% respectively at 10 years[62]. These results have not been obtained in large series with bladder preservation treatments for equivalent stages (see below). Cystectomy provides the largest reduction in the risk of cancer-specific and nonspecific death in patients over 80 years of age[63]. The largest single-institution retrospective study on cystectomy available to date showed that patients over 80 years of age had greater postoperative morbidity, but not greater mortality[64].

Despite the fact that preoperative RT in patients with operable muscle-invasive BC results in tumor downstaging after 4-6 weeks, this practice is not recommended to improve survival (grade of recommendation: B)[65].

Palliative cystectomy in muscle-invasive bladder cancer

Palliative cystectomy with urinary diversion using intestinal segments is performed in patients with locally advanced pelvic cancer and bladder involvement for the relief of symptoms such as pain, recurrent bleeding, urgency or fistula formation[66]. In patients with inoperable locally advanced tumors (pT4b), primary RC is not recommended as a primary curative treatment option (grade of recommendation: B). The only indication for palliative cystectomy is to relieve symptoms, and morbidity of surgery and QoL should be weighed against other options (grade of recommendation: B/C; LE: 3).

Bladder-sparing treatments

In most patients with localized BC, TUR, RT or chemotherapy alone are not indicated as a primary curative treatment option (grade of recommendation: B). Favorable long-term survival rates have been reported with multimodal treatment methods combining TUR, RT, and chemotherapy[41,67-69]. However, a bladder-preserving multimodal strategy requires very close multidisciplinary cooperation and high level of patient compliance. Even if a patient has a complete response to multimodal treatment, the bladder remains a potential source for tumor recurrence. About half of the patients can expect to preserve their native bladder intact. After completing multimodal treatment, a T0 status in repeated TURs is considered a factor of great prognostic value[67,70]. However, even patients with the best prognosis have a life-long risk of intravesical tumor recurrence, requiring meticulous monitoring and multiple invasive procedures. It appears that delay in RC due to an initial bladder-preserving treatment increases the risk of lymph nodes metastases to a lymph node-positive rate of 26%, when cystectomy is required due to failure of conservative treatment (LE: 2b). Currently, multimodal therapy in localized disease is only considered as an alternative in selected, well-informed and motivated patients where cystectomy is not considered for clinical or personal reasons (grade of recommendation: B).

Chemotherapy in nonlocalized bladder cancer

Adjuvant chemotherapy

To date, only 5 randomized trials and 1 meta-analysis have been published on adjuvant chemotherapy, with updated individual patient data from 6 trials and a total of 491 patients for survival analysis[37,71-75].

Furthermore, all these studies are suboptimal with significant deficiencies, such as small sample size, use of substandard chemotherapy, early termination of patient recruitment and flaws in design and statistical analysis, including irrelevant endpoints or absence of recommendations on salvage chemotherapy for relapses or metastases[76]. The data are not consistent enough to give a clear recommendation on the use of adjuvant chemotherapy (LE: 1a). Consequently, adjuvant chemotherapy is only included in clinical trials, but not for routine use, since it has not been sufficiently studied (grade of recommendation: A).

Chemotherapy in metastatic disease

Bladder cancer is a chemosensitive tumor. Response rates vary according to various patient- and disease-related characteristics. Single-agent chemotherapy provides a low response rate and this is generally short term (LE: 2a).

Prognostic factors for response and survival are known[77]. Cisplatin-based combination chemotherapy has been the standard treatment since the end of the 1980s. Methotrexate, vinblastine, doxorubicin (adriamycin), and cisplatin (MVAC) and gemcitabine/cisplatin (GC) have prolonged survival up to14.8 and 13.8 months, respectively[78-81].

Although equivalence has not been studied, neither of the combinations was shown to be superior over the other, with response rates of 46% and 49% for MVAC and GC, respectively. Long-term survival results confirmed the suspected equivalence of the two regimens. The major difference between the two combinations was toxicity, with GC being less toxic. With cisplatin-based combinations, patients with lymph node metastases only, good PS and good renal function may achieve excellent response rates, including a high rate of complete responses, with disease-free survival in up to 20% (LE:1b)[33,78,82,83] Carboplatin-containing combinations are less effective than cisplatin-based chemotherapy in terms of complete response and survival (LE: 2a).

Other non-cisplatin containing chemotherapy combinations have provided good responses in first- and second-line use, both in fit patients or unfit patient groups, but these combinations have not been tested against standard chemotherapy (LE: 2a). Small-sized phase II trials provide evidence of moderate response rates for single agents or non-cisplatin-containing combinations in second-line use (LE: 2a). Postchemotherapy surgery after partial or complete responses may improve 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 (LE: 3).

The indication for treatment and patient selection are decided based on the prognostic factors (grade of recommendation: B). The first-line treatment for fit patients should be cisplatin-containing combination chemotherapy with GC, MVAC (preferably with granulocyte-colony stimulating factor [GCSF]), or high-dose MVAC with GCSF (grade of recommendation: A). Carboplatin and non-platinum combinations as first-line treatment in patients fit for cisplatin are not recommended (grade of recommendation: B), except in patients unfit for cisplatin (grade of recommendation: C). Data are insufficient at present to support a recommendation

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

Condition	Conclusion or recommendation	LE or grade of recommendation
Secondary urethral tumor	Staging and treatment should be done as for primary urethral tumor	3
	In non-invasive tumors, 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 procedures for 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 treatment options (alone or in combination)	C
Upper urinary tract recurrence	Specific upper urinary tract imaging is only indicated in case of symptoms. Radical nephroureterectomy may prolong survival	B

LE level of evidence; RT: radiotherapy.

for standard second-line chemotherapy. Therefore, second-line treatment should be considered in the context of a clinical trial. In this situation, paclitaxel/gemcitabine or a single agent should be considered if the patient has a good PS (grade of recommendation: C).

Follow-up of patients with muscle-invasive bladder cancer

The authors wish to emphasize the fact that any recommendation on follow-up is entirely based on expert consensus and data with a level of evidence of 4. An appropriate schedule for disease monitoring should consider the natural history of recurrence, the probability of disease recurrence, the functional impairment of specific organs, and the possibilities of treatment of a recurrence[84]. In general, the period of oncological surveillance can be concluded after 5 years of follow-up, but it is advisable to continue surveillance directed specifically to functional aspects related to the type of urinary diversion and the general condition of the patient. Recommendations and suggestions on overall aspects of follow-up in different stages and specific situations are described in Tables 4 and 5.

The prognosis of a patient with a pelvic recurrence depends on the type of recurrence. Systemic chemotherapy, local salvage surgery or radiotherapy can increase survival in some cases, but provides significant symptom improvement in most patients.

Distant metastases occur in up to 50% of patients treated with cystectomy. Most occur in the first 24 months, although cases of progression have been reported after 10 years of follow-up. Pathological stage and lymph node involvement are risk factors. The most common sites of distant metastases are the lungs, liver, and bones[85]. Upper urinary tract recurrences are uncommon (2-7%), but when they occur, they usually develop in the first 22-40 months after cystectomy[56,84,85]. Surveillance regimens usually fail to detect these tumors before the onset of symptoms. However, radical nephroureterectomy can prolong survival[86].

The incidence of urethral recurrence is 5-17%, and it is particularly common between the first and third year after surgery. Prophylactic urethrectomy during cystectomy is not justified in most patients. In men, the most important risk factor for the development of urethral recurrence is prostate stromal invasion (21-64%)[87,88]. In women, the risk factor is the presence of tumor in the bladder neck[89]. Multiple studies demonstrate that the risk of urethral involvement after orthotopic diversion (0.9-4%) [87,90,91] is significantly less than after nonorthotopic diversion is performed (6,4-11,1%). Routine performance of urethral washes and urine cytology does not appear to have any beneficial effect on survival[92,93].

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Table 5 – Suggestions for follow-up based on initial tumor stage postcystectomy

	Months postcystectomy								
	3	6	12	18	24	30	36	48	60
< pT1									
Renal ultrasonography	×	–	–	–	–	–	–	–	–
CT/MRI Cht/Abd + UUT *	–	–	×	–	×	–	×	×	×
Lab **, sed, culture and cytology	×	×	×	–	×	–	×	×	×
pT2									
Renal ultrasonography	×	–	–	–	–	–	–	–	–
CT/MRI Cht/Abd + UUT*	–	×	×	×	×	–	×	×	×
Lab **, sed, culture and cytology	×	×	×	–	×	–	×	×	×
> PT3 o N+									
Renal ultrasonography	×	–	–	–	–	–	–	–	–
CT/MRI Cht/Abd + UUT*	×	×	×	×	×	×	×	×	×
Lab **, sed, culture and cytology	×	×	×	–	×	×	×	×	×

*Retrograde ureteropyelogram with selective urine collection from the upper urinary tract should be performed; **blood tests, including serum creatinine or renal function test and blood gases; abd: abdominal; CT: computed tomography; MRI: magnetic resonance; lab: laboratory tests; sed: urinary sediment; cht: chest; UUT: upper urinary tract.

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