# UPDATE: DIAGNOSIS AND TREATMENT OF MUSCLE-INVASIVE AND METASTATIC BLADDER CANCER IN 2014

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## ABSTRACT

Bladder cancer (BC) is the ninth most commonly diagnosed malignant tumour in the world, with an incidence of about 356,000 and a mortality of about 145,000 per year in both non-muscle-invasive and muscle-invasive BC. Although a high percentage of urothelial cancers of the bladder are staged as non-muscle-invasive, muscle invasion can already be found in about 30% of all patients at the time of initial diagnosis. The intention of the following article is to give an overview of the diagnosis and treatment of muscle-invasive and metastatic BC according to the latest update of the EAU (European Association of Urology) guidelines.

Keywords: Muscle-invasive bladder cancer, diagnosis, treatment, radical cystectomy, urinary diversion, metastatic bladder cancer, chemotherapy, follow-up.

## INTRODUCTION

Currently bladder cancer (BC) is the second most commonly diagnosed urological tumour. Therefore, guidelines and updates on diagnosis, surgical, oncologic, as well as palliative treatment are of great importance. The latest EAU (European Association of Urology) guidelines on muscle-invasive and metastatic BC represent a generally accepted recommendation regarding those issues based on recent study data. The intention of the following article is to give an overview of the diagnosis and treatment of muscle-invasive and metastatic BC according to the latest update of the EAU-guidelines.[1]

### Aetiology and Risk Factors

Smoking tobacco is the most known risk factor for urothelial BC. Overall, 50-65% of men and 20-30% of women with BC have a positive history of smoking.[2] Although BC is found more often in men than in women (3.8:1),[3] muscle-invasive tumour stage is more often found in women compared to men at initial diagnosis.[4] In addition, occupational exposure to benzoyl derivatives and aromatic amines has been identified as a risk factor causing about 20-25% of all urothelial BC.[5,6] Fortunately exposure rates to these toxic agents have been decreasing in the Western world over recent years. Also, radiation, bilharzia, chronic infections, and chemotherapy can be found as risk factors in literature; they are often associated with histopathological entities other than urothelial BC (e.g. squamous cell BC).[7-9]

## DIAGNOSIS

In most patients with urothelial BC, painless haematuria is the first symptom. Furthermore, pelvic and gastrointestinal pain, as well as voiding problems, may be found depending on clinical stage. In addition to ultrasound of the urinary tract, cystoscopy plays a central role within the diagnostic workup, which can be supplemented by urinary cytology. Afterwards, transurethral resection of bladder tumour (TURB) is used for histopathological confirmation. TURB might even be performed without having a previous cystoscopy if a tumour has already been found by imaging previously. The use of photodynamic diagnostics (PDD) increases the chance of finding a tumour, especially flat tumours such as carcinoma *in situ* (CIS). However, there might be an increased rate of false-positive findings.[10,11] The surgeon must achieve a muscle-deep resection of the tumour during TURB

in order to enable the pathologist to differentiate between non-muscle-invasive (NMIBC) and muscle-invasive bladder cancers (MIBC). According to the initial tumour stage (pTa high grade, CIS, pT1), resection should be repeated after 2-6 weeks because of the risk of a residual tumour.[12] In special situations, such as tumours in close contact to the urethra or multifocal CIS, an additional biopsy of the prostatic urethra is recommended.[13] This can be done during TURB or radical surgery by frozen sections.[14] A simultaneous prostate cancer can be found in 25-46% of male patients undergoing radical cystoprostatectomy.[15]

Radiological techniques such as computer tomography (CT) and magnetic resonance imaging (MRI) are routinely used for tumour searches in the upper urinary tract as well as for the staging of MIBC. Therapeutic options as well as prognosis correlate closely with tumour stage and grade of differentiation.[1,16] Although MRI and CT both have deficiencies in evaluating infiltration of the perivesicular fat tissue, both methods provide reliable information regarding the extent of local tumour invasion into nearby anatomical structures.[17] Both techniques have shown similar sensitivity for the detection of enlarged lymph nodes. However, their diagnostic accuracy for metastases in minimally enlarged or normal-sized lymph nodes is limited. Furthermore, CT and MRI are routinely used to detect distant peritoneal, pulmonary, adrenal, osseus, brain, or liver metastases. By now, CT or MRI is recommended for staging locally advanced or metastatic disease in patients for whom radical treatment is being considered.[1]

Due to poor survival and modest disease control rates, different biomarkers have emerged as a promising tool for prognosis and treatment selection in patients with urothelial cancer. Usually those markers are measured at DNA, RNA, or protein level. Various novel molecular markers have been investigated within the pathological assessment so far as, for example, FGFR3-mutation status, TP53, Ki-67, and CK20. Although the numbers of those biomarkers are constantly growing, the clinical relevance is unclear due to a lack of independent validation on external datasets.[18-21] Therefore, none of those biomarkers can be recommended for routine use in daily clinical practice at this time.[1]

## TREATMENT OPTIONS

### Failures in NMIBC

The diagnosis of a NMIBC is generally associated with the possibility of understaging and the risk of tumour progression. This can be up to 50% at the time of initial diagnosis.[22] Pathological grading is a key factor for describing the severity of bladder cancer. According to the World Health Organization classification of 2004, grading of urothelial cancer differentiates between low and high-grade tumours. Therefore, a new category for high-risk NMIBC patients has been developed for those who should undergo radical cystectomy, including pT1 high grade, CIS, and/or pTa (but only in case of recurrence of multiple large tumours) tumours.[22-24] Although there is an ongoing debate on the effectiveness of intravesical Bacillus Calmette-Guérin (BCG) therapy in delaying progression in high-risk NMIBC, a recent multicentre trial showed lower progression rates, even in the presence of a concomitant CIS.[25] According to the latest EAU guidelines, immediate radical treatment is an option in all tumours at high risk of progression (recommendation Grade C). In case of BCG failure, radical treatment should be offered to the patient and performed within 9 months (recommendation Grade B).[1,22]

### Neoadjuvant Chemotherapy and Preoperative Radiotherapy

Since 5-year survival rates after radical treatment of localised MIBC are only about 50%, neoadjuvant chemotherapeutic approaches (NAC) have been used in order to treat micrometastatic disease, and hence, improve overall survival (OS). Nevertheless, the overtreatment of patients without micrometastatic disease must be discussed as it represents a major drawback of those neoadjuvant approaches. In order to overcome this problem, early preoperative identification of NAC responders utilising molecular tumour profiling in TURB specimens might be performed in future; however, there is still a lack of reliable data.[26] Furthermore, radical cystectomy might be delayed in non-responders, compromising their final outcome. Within the neoadjuvant scheme a better tolerability of chemotherapy is expected compared to a post-surgery administration.[1] Three independent meta-analyses have shown a benefit in OS of 5% for cisplatin-based neoadjuvant chemotherapy, with an absolute disease-free survival rate of 9% at 5 years.[27-29] Nevertheless it must be stated that

the data concerning neoadjuvant chemotherapy schemes is very limited to date. In the case of progression under neoadjuvant chemotherapy, this treatment should be discontinued and the patient should undergo radial cystectomy immediately. Up-to-date neoadjuvant cisplatinum-based chemotherapy is recommended for patients with pT2-4a, cN0, M0 tumours, good performance status, and normal renal function (recommendation Grade A).[1] Especially in patients with complete response to neoadjuvant chemotherapy (pT0 N0 in the radical cystectomy specimen), neoadjuvant chemotherapy has a major impact on OS.[30] In addition, the early assessment of treatment response by imaging represents another difficulty within a neoadjuvant approach. Among others, PET-scan and dynamic contrast-enhanced MRI have been tested in small study groups; however, there are no adequate data for a common recommendation so far.[31,32] Proper selection of patients who will respond to neoadjuvant chemotherapy is difficult in current routine clinical practice due to the lack of unequivocal biomarkers or a widely applicable test. Future developments towards a personalised medicine might help to overcome those problems.

At this time, data on the effectiveness of preoperative radiotherapy are very rare. Also, while tumour downstaging might be achieved by preoperative radiotherapy, no improvement of survival has been demonstrated so far.[1,33] Therefore, no recommendation can be made for preoperative radiation therapy.

## Radical Cystectomy and Urinary Diversion

In the case of MIBC, radical cystectomy is the curative treatment of choice. Radical cystectomy should be performed early within 3 months after histopathological confirmation by TURB, as outcome and survival are reduced otherwise, except within a neoadjuvant chemotherapeutic approach.[34,35] Lower morbidity and mortality rates have been observed for surgeons and hospitals with a high caseload.[36] In terms of decision-making and postoperative complication rates, performance status,[37] comorbidities, biological age, and preexisting comorbidities have been identified as important factors. In order to estimate the individual perioperative morbidity and mortality, different scores have been developed.[38,39] As the American Society of Anesthesiologists Score (ASA-Score) does not address comorbidities, it should not be used in the setting of radical cystectomy.[1,40] In contrast to that, the age-adjusted Charlston Comorbidity Index was shown to be an independent prognostic marker for cancer-specific mortality,[37] perioperative mortality,[41,42] and overall mortality.[43,44] Bilateral regional lymph node dissection (LND) is essential in terms of surgical staging. Even though lymph node metastases are very unlikely outside the true pelvis, the extent of LND is still under debate as some studies support the idea that an extended LND might improve outcome after radical cystectomy.[45-49] Nevertheless those studies contain significant limitations, therefore, more data are needed to make a clear recommendation. Laparoscopic or robot-assisted cystectomy with following intracorporal reconstruction of urinary diversion must still be judged experimentally as these techniques are not used routinely so far, and data on long-term outcome are lacking.[1]

Overall four techniques of urinary diversion are routinely used: incontinent cutaneous, continent cutaneous, and orthotopic, as well as rectosigmoid diversions. The proper choice of diversion depends on individual factors such as performance status, age, and comorbidities as well as the skills of the surgeon.[2,36] Especially in elderly patients, a careful decision-making process is very important.[50] Basically, a distinction can be made between wet (e.g. ureterocutaneostomy, ileal conduit) and dry urinary diversions (e.g. orthotopic bladder substitution/neobladder, Mainz-Pouch, Indiana-Pouch). Each urinary diversion includes its own problems. The ileal conduit is a well-established and widely-used option. Nevertheless typical complications (infections, uretero-ileal stenosis, stomal problems) may develop over time.[1] Although ureterocutaneostomy is surgically less challenging with lower perioperative complication rates, late infections of the upper urinary tract and stricturing on skin level are more frequent compared to ileal conduit.[51-53] Continent cutaneous diversions such as the Mainz or Indiana-Pouch are associated with clear benefits as they provide satisfying continence both day and night for the majority of patients.[54] However, deterioration of renal function, strictures, ureterorenal reflux, stomal complications (stenosis versus incontinence), as well as stone formation within the pouch (especially if staples have been used) have been described. Over the last few years orthotopic bladder substitution has become a safe technique with compelling long-term results in both men and women.[55] According to current literature there are no differences regarding quality of life in patients with neobladder compared

to those with an ileal conduit.[56] Specific long-term complications of the neobladder technique are incontinence during day (8-10%) and night (20-30%), ureterointestinal stenosis (3-18%), and urinary retention (4-12%) in both genders. Furthermore, malabsorption problems (e.g. vitamin B12 deficiency) and metabolic disorders (e.g. hyperchloraemic acidosis) may occur.[51-57]

## Palliative Cystectomy and Supportive Care

In the case of locally advanced tumours, severe complications can develop over time, including heavy pain, bleeding, and urinary/intestinal obstruction. Due to the fact that radical cystectomy has the greatest morbidity of all therapeutic options within such a setting, it should only be performed if there are no other options.[58] Severe bleeding of the bladder can be treated by transurethral coagulation or bladder lavage with silver nitrate or alum. In case of obstruction, urinary diversion might be performed without radical cystectomy.[59] In addition, radiation can be used for palliative care of bleeding and pain.

## Bladder Sparing Approaches in Localised Disease

TURB is not a curative option for MIBC in general. However, TURB might constitute as a treatment option for patients unfit for radical cystectomy and localised invasive disease (max. pT2) after negative re-TURB.[1] External-beam radiotherapy is also a possibility for patients unfit for surgery; however, the cancer specific survival is lower compared to radical cystectomy. A multimodal combination of treatment modalities (e.g. external beam radiation with concurrent chemotherapy) showed higher disease specific survival rates than radiation alone.[60] According to the latest EAU-guidelines, multimodal treatment could be offered as an alternative method in selected, well-informed, and compliant patients, especially for whom radical cystectomy is not an option.[1]

## Adjuvant Chemotherapy and Metastatic Disease

By now there is no general recommendation for adjuvant chemotherapy within a routine therapeutic regimen as no improvement in OS has been shown in this setting. Furthermore, the ideal time for adjuvant chemotherapy (immediate treatment versus treatment at the time of relapse) is still unclear due to a lack of sufficient clinical data. The absence of a measurable tumour load as well as the delay of chemotherapy caused by perioperative morbidity represent the key disadvantages of an adjuvant setting.[1] In the last few years, therapeutic options for palliative care in metastatic BC have increased. 30 years ago the OS of metastatic BC was only 3-6 months.[61,62] Since the 1980s, chemotherapy schemes containing cisplatin (gemcitabine-cisplatin (GC) or methotrexate-vinblastine-doxorubicin [Adriamycin]-cisplatin [M-VAC]) have demonstrated prolonged survival rates compared to cisplatin monotherapy, and have, therefore, been used routinely. Both have shown prolonged survival rates up to 13.8 and 14.8 months respectively, compared to cisplatin monotherapy. However, equivalence of GC versus MVAC has not been tested, also, neither of those two combinations is superior to the other with similar response rates (49% versus 46%).[63,64] Due to lower toxicity rates and equal effectiveness, GC is still the preferred option.[64,65]

Tolerance of the MVAC-scheme can be enhanced by combination with granulocyte colony stimulating factor (G-CSF).[66] Lower toxicity rates have been reported for the use of high-dose MVAC (HD-MVAC) in combination with G-CSF compared to standard MVAC. Also efficacy was higher in terms of dose density, complete response rates, and 2-year survival rate, although no significant difference in median survival has been shown between the two regimens.[67] The new paclitaxel-cisplatin-gemcitabine triple scheme did not result in a significant improvement in OS compared to GC.[68,69] According to the EAU-guidelines, GC, PCG, MVAC, and HD-MCAV remain the treatment of choice in patients with metastatic urothelial cancer eligible for cisplatin. Non-cisplatin-based chemotherapy schemes are not recommended for first-line use in patients who are fit enough for cisplatin at the moment.[2] Worse outcome rates have especially been reported for patients with low performance status prior to chemotherapy (<80%) or visceral metastases.[70] Age is a negligible factor regarding response to chemotherapy or toxic events caused by chemotherapy.[71]

In patients unfit for cisplatin-based chemotherapy (because of poor performance status, impaired renal function, or other relevant comorbidities) a combination of gemcitabine with the less toxic agent carboplatin can be offered.[72,73] In case of a delayed relapse (>6-12 months) after first-line chemotherapy, a re-challenge with a cisplatin-based scheme might be discussed with the patient. Patients with metastatic disease progressing early

after platinum-based combination chemotherapy should be offered a second-line treatment with vinflunine, which is currently the only European Medicines Agency (EMA)-approved agent in the second-line setting. The approval is based on a recent trial comparing vinflunine with best supportive care against best supportive care alone, which showed an acceptable safety profile in combination with a statistical survival benefit for the eligible patient group, despite a modest overall response rate of 8.6%.[1,74]

Bone metastases can be found in 30-40% of patients with MIBC or NIMBC.[75] Therefore, an osteoprotective therapy with denosumab or zoledronic acid should be carried out in order to prevent skeletal related events such as the risk of fracture or osseous pain.[76] In addition, supplementation with vitamin D and calcium is recommended. In case of impaired renal function, the dosage of zoledronic acid must be adjusted.

## Follow-Up

All patients with MIBC or metastatic BC must undergo a close oncologic and functional follow-up, taking into account the probability of relapse and possible palliative treatment options. A systematic follow-up scheme based on the stage of the initial tumour after radical cystectomy has been suggested by Stenzl et al.[77] (Table 1). Both local and distant recurrence typically occurs within 2 years after initial surgery, preferably in patients with higher initial tumour stage and locally advanced tumours.[78,79] Pelvic recurrence can be found in 5-15% of all patients. Options are limited within this palliative setting with infaust prognosis.[1] Distant metastases typically occur in the lungs, bones, and liver. Therefore a sufficient follow-up must be adapted individually to each patient. On the one hand, it has to address oncologic aspects such as local recurrence and occurrence of distant metastases, on the other hand, functional aspects associated with the different types of urinary diversion. Relapse of urothelial cancer in the upper urinary tract is possible though very rare. The same applies for secondary urethral tumours, which typically occur 12-36 months after radical cystectomy. In both cases radical surgery may be performed with curative intention in non-metastatic patients depending on the stage at the time of presentation.[1,80] In conclusion, a lifelong follow-up is indispensable in MIBC or metastatic BC, and must be adjusted, individually addressing all oncologic as well as functional aspects.

**Table 1: Suggestion for general follow-up based on the stage of initial tumour after radical cystectomy.**

| Procedure | Months after radical cystectomy | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **≤pT1** | 3 | 6 | 12 | 18 | 24 | 30 | 36 | 48 | 60 |
| Ultrasound kidneys | x | | | | | | | | |
| CT/MRI thorax/abdomen including UUT* | | | x | | x | | x | x | x |
| Lab, sed, culture, cytology | x | x | x | | x | | x | x | x |
| **pT2** | | | | | | | | | |
| Ultrasound kidneys | x | | | | | | | | |
| CT/MRI thorax/abdomen including UUT* | | x** | x | x** | x | | x | x | x |
| Lab, sed, culture, cytology | x | x | x | | x | | x | x | x |
| **≥pT3** | | | | | | | | | |
| Ultrasound kidneys | x | | | | | | | | |
| CT/MRI thorax/abdomen including UUT* | x | x | x | x | x | x | x | x | x |
| Lab, sed, culture, cytology | x | x | x | | x | x | x | x | x |

CT: computed tomography scan; MRI: magnetic resonance imaging; Lab: laboratory tests (blood chemistry including serum creatinine or renal function and blood gas analysis); sed: urine sediment analysis; UUT: upper urinary tract.

* If pathological UUT finding in CT or positive cytology, recurrent primary sampling should be performed.

** T2a, N0M0 tumours and/or Karnofsky score <100%.

*Modified from Stenzl et al.[8]*

## CONCLUSION

Over the last few years, diagnostic and therapeutic approaches in MIBC and metastatic BC have significantly changed. Neoadjuvant chemotherapy schemes have found their way into daily clinical use in case of pT2-4a, cN0M0 tumours. Nevertheless, the selection of patients who will respond to neoadjuvant chemotherapy is still difficult. In future, biomarkers and genetic tests will hopefully provide a sufficient tool for estimation of prognosis and treatment selection in patients with urothelial cancer of the bladder, opening up the way towards a more personalised medicine setting. Furthermore, those tests might help to establish targeted therapy approaches as well as to improve quality of life during tumour therapy. Systematic schemes can be used for follow-up but should be adapted individually to each patient.

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