

# Management of muscle invasive, locally advanced and metastatic urothelial carcinoma of the bladder: a literature review with emphasis on the role of surgery

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**Abstract:** Locally advanced (T3b, T4 and N1–N3) and metastatic urothelial bladder cancer (BCa) is a lethal disease with poor survival outcomes. Combination chemotherapy remains the treatment of choice in patients with metastatic disease and an important part of treatment in addition to radical cystectomy (RC) in patients with locally advanced tumour. Approximately half of patients who underwent RC for muscle invasive BCa relapse after surgery with either local recurrence or distant metastasis. This review focuses on the management of muscle invasive, locally advanced and metastatic BCa with emphasis on the role of surgery; to summarize the current knowledge in order to enhance clinical decision-making and counselling process.

**Keywords:** Bladder cancer (BCa); metastatic bladder cancer; locally advanced bladder cancer (ABC); radical cystectomy (RC); metastasectomy

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## Introduction

Urinary bladder cancer (BCa) accounts for about 5% of all new cancers in the United States with estimated 74,960 new cases and 16,390 deaths in 2016 (1). Rates for new BCa cases have been decreasing on average by 0.8% per year over the last 10 years; death rates have been, on the other hand, stable over 2004–2013. The 5-year Relative Survival has only marginally improved from 71.5% to 77.5% from 1975 to 2008 (2), indicating a gap between diagnosis and management of these patients. Indeed such minor improvement is likely due to other reasons

than improvements in treatment (3,4). Today, in western countries still, 10–15% of BCa patients present with metastatic disease (5). In addition, nearly half of patients with muscle-invasive bladder cancer (MIBC) will eventually relapse after radical cystectomy (RC) (6). Almost all patients who succumb to BCa have disseminated and often symptomatic metastasis at time of death (7,8). Generally, the outlook of these patients is poor and treatment is mostly palliative in nature. It is worthwhile to mention that there are no major advances achieved in the last three decades but newer advances such as immunotherapeutic and targeted

therapies promise to change this status quo significantly. To understand how to help patients today best and to assess the possible interactions between today's and tomorrow's therapies, there is a need for well-designed analysis of our current knowledge of the natural history of this disease state, of available treatment strategies and of possible therapeutic alternatives for this subset of patients (9,10).

### Overview of management of muscle invasive BCa

RC with pelvic lymph node dissection (PLND) is the standard treatment for patients with non-metastatic MIBC (cT2-T4a, cN0-Nx, M0) (6) and patients with very high-risk non-muscle invasive BCa (11). The 5-year overall survival (OS) rates were estimated to be around 60% (12-14), ranging from 32% in patients with lymph node involvement to 75% in those without (15). RC includes pelvic lymphadenectomy as an integral part of the procedure with better oncological outcomes in patients with N0M0 MIBC. Indeed, lymph node status is the single most powerful pathologic predictors of long term disease-specific survival (DSS) and OS, but the exact extent of PLND is a matter of debate with on-going randomized trials adding new knowledge soon (13,14,16,17). Despite radical treatment, the incidence of distance failure in clinically non-metastatic patients with organ confined, extravesical and lymph node positive disease were estimated to be 25%, 37% and 51%, respectively (18). This is attributed to the presence of micrometastasis that remains undiagnosed at the time of surgery (14).

About one fourth of patients who undergo RC and PLND have concomitant lymph node metastasis; the rate of involvement increases with increasing tumor stage (14,17,19). Node positive disease carries a worse prognosis with 5-year recurrence-free survival (RFS) rates in the range of 4–35% (13,14,17). RC with extended PLND alone can provide long term RFS in approximately 25% patients with lymph node metastasis. However, this is mostly true in a small subgroup of lymph node positive patients with localized disease and limited lymph node metastatic burden. Consequently, this finding does not obviate the need of perioperative systemic therapy (14,20). Before discussing management strategies of MIBC, locally advanced and metastatic BCa, it is prudent to mention that a radiological evaluation should take place before any treatment with curative intent to accurately stage the disease and to identify patients with locally advanced and/or metastatic disease. The EAU guidelines recommend computed tomography

(CT) of the chest, abdomen and pelvis as the optimal radiological staging for patient with MIBC. Accurate clinical staging is of utmost importance for patient counselling, prognostication and treatment planning. Unfortunately, up- and down-staging are not uncommon existing in a range of 27–62%. This discrepancy between clinical and pathological staging is caused partially by inaccuracy of radiological tools and represents one of the most important barriers to improvement treatment strategies (19,21).

It is also important to emphasize the importance of accurately predicting patient prognosis and the expected outcome of selected treatment for proper counselling and treatment planning. These information are fundamental for treating physicians and patients, especially when based on solid and comprehensive data. A well-informed patient can take part in decision-making process depending on individualized risk estimation. Developing and adopting validated nomograms (especially when incorporating molecular markers) represent major advancement in this field as it provides more discriminating and accurate predicting tool over the currently adopted AJCC staging system which relies only on stage, lymph node status and presence of metastasis (7).

### Role of neoadjuvant chemotherapy (NAC)

In the landmark phase III randomized intergroup clinical trial conducted by the Southwest Oncology Group (SWOG S8710) in patients with MIBC T2–T4aN0M0, Grossman *et al.* demonstrated that the estimated risk of death is reduced by 25% in patients receiving three cycles of M-VAC NAC plus RC compared to RC alone. The trial also proved that patients who had been down-staged to pT0 had a better survival than those who did not achieve complete response (22). An update of the advanced bladder cancer (ABC) meta-analysis collaboration systematic review and meta-analysis based on 11 trials with 3,005 patients supported this beneficial effect of NAC over definitive local therapy alone with a 14% reduction in the estimated risk of death compared to definitive local therapy alone. This is also equivalent to an absolute survival benefit of 5%, improving OS from 45% to 50% at 5 years (23). NAC was not associated with increased risk of death, did not affect the patients' chance of undergoing RC (22) and did not increase perioperative morbidity (22,24,25). Despite that and the compelling level 1 evidence, NAC is still underutilized and treatment is often with RC alone or RC with adjuvant chemotherapy (AC) (26,27).

### The effect of surgical factors on local recurrence and survival outcomes

Herr and colleagues performed secondary analysis of the patients who had RC in the SWOG 8710 trial with the aim of identifying the surgical variables associated with survival outcomes. The investigated variables were margin status, total number of lymph nodes examined, extent of PLND, type of institution (academic, community, or Veterans Affairs), type of urinary diversion and whether the surgeon was a general urologist or an onco-urologist. They found that surgical variables were associated with local recurrence and survival outcomes in patients with locally advanced BCa whether or not they received NAC. Positive surgical margins and number of lymph nodes removed (cutoff of 10) were found to be independently associated with local recurrence and worse survival after adjusting for the effects of treatment type, pathological stage and lymph node status. Testing the association between treatment and number lymph nodes removed or margin status was not statistically significant. Type of surgeon and institution were not associated with local recurrence or OS survival. Nevertheless, when number of lymph node removed and the status of margin were tested in a multivariable model adjusted for the effects of other variables, the type of surgeon (general urologist) and the institution (non-academic) independently predicted removal of less than ten lymph nodes and positive surgical margins. Similarly, type of surgeon and institution were also associated with type of diversion with less experienced centers tending to ileal conduits more often. PLND as a variable was not found to be independently associated with survival and local recurrence; the authors suggested that the numbers of lymph nodes are more accurate than the extent of PLND (28).

The results of this secondary analysis were interesting in different ways. First, this analysis suggested that the quality of surgery influenced the oncological outcomes; it was indeed more important than whether patients received NAC or not. Secondly, the quality of surgery was influenced by the work focus of the surgeon and the type of institution. Third, NAC treatment did not affect the surgical factors. These findings address important aspects in our efforts to improve cancer management, not only in BCa, but also other tumors such as surgical training with greater emphasis on the role of well-structured training programs, sub-specialty training, quality control of oncological surgery, referral to high volume center and/or surgeons, and adding the quality of surgery into future models to measure the actual effect on treatment.

### Clinically positive lymph nodes

Although NAC has been shown to be associated with improved survival in randomized clinical trials (22,23,29), most trials did not include patients with clinically node positive disease (cN1-3). For example, the ABC Meta-analysis Collaboration included only 4% of patients with cN1/cN2 and 48% with unknown N stage (cNx). In patients with clinically positive lymph node metastasis, systemic chemotherapy may be given as the primary therapy followed by RC with bilateral PLND as a consolidation therapy only in those patients who achieve notable response (30). A multi-center analysis of the outcomes of 304 patients with clinically positive lymph nodes who underwent primary chemotherapy using different regimens and RC as a consolidation therapy showed that almost half of patients achieved pN0 and about one quarter converted to pT0 after induction six cycles instead of three or four cycles chemotherapy. The pathological complete response (pCR) rate was 14.5%. The median OS was 22 months and survival was significantly better for patients who achieved complete nodal response, had negative surgical margins at time of RC and underwent excision of 15 or more lymph nodes. In addition, there was no statistically significant difference in outcomes between the MVAC and the GC regimen (30). Nieuwenhuijzen *et al.* evaluated the response and survival outcomes of 52 patients with histologically proven lymph node metastasis treated with chemotherapy followed by post chemotherapy surgery after achieving partial or complete response. Complete response was independently associated with DSS yielding 5-year survival rates of 42%. Additionally, lymph node response was found to be more important than local tumor response as no patient with node positive disease after chemotherapy achieved 2-year survival. Even in patients with partial response, post-chemotherapy surgery resulted in 5-year DSS of 19% (31). Other studies described higher rates of pCR (32,33) and lower OS time (31,33).

### The effect of complete clinical and pathological response

In a study that described the natural history in 109 patients who achieved complete clinical response after combination cisplatin-based chemotherapy, 29% achieved cT0. Then, 7 patients chose immediate RC and 25 chose active surveillance. Three fourth of patients who opted for surveillance preserved their bladder at a median follow up time of 55 months with CSS rates of 88% at 5 years

including patients who underwent delayed RC for disease recurrence or progression. Immediate RC was not found to be significantly different from delayed RC in term of survival outcomes. However, this study has to be judged with caution because of its small sample size and possible selection bias. Nevertheless, it supports the importance of prediction of outcomes in patients who achieve cT0; as this is a heterogeneous population with a proportion benefitting from bladder-sparing active surveillance and others needing completion RC to ensure long term survival (34). Of the 126 patient who received three cycles of NAC in the SWOG S8710 trial, 38% of the surgical specimens were (pT0) (22). A meta-analysis of 13 trials evaluating the effect of pCR in primary tumor as well as lymph nodes after NAC showed that a pCR rate of 29% and a relative risk for RFS of 0.19 ( $P < 0.00001$ ) and for OS of 0.45 ( $P < 0.00001$ ) (35). These data underline the efficacy of cisplatin-based combination chemotherapy and for now the need for completion RC until better stratification is possible.

### Intraoperative finding of enlarged lymph nodes

Herr *et al.* reported on a series of 84 patients with grossly enlarged resectable lymph node at time of RC and PLND. The median survival was 19 months and about one fourth of patients achieved long term survival of 10 years. They concluded that if PLND can be performed completely and safely, it is better to proceed with RC and PLND (36).

### AC

An updated systematic review and meta-analysis of nine randomized controlled trials that included 945 patients demonstrated survival advantages in patients who received AC; 22% and 34% relative reduction in the risk of death and disease recurrence, respectively. Interestingly, there was a greater absolute benefit among those with positive nodal involvement in terms of disease-free survival (37). Also, a large international study that included more than 1,500 patients with lymph node positive disease after RC reported 17% relative risk reduction in CSS in those who received adjuvant cisplatin-based combination chemotherapy compared to those who underwent surgery alone (26). A randomized trial that recruited 284 patients showed no significant OS benefit in patients receiving immediate AC in comparison to patients who received deferred chemotherapy (at time of relapse) in pT3–pT4 and/or node positive (pN1–3) M0 disease. Nevertheless, a significant PFS

advantage was noted in favor of immediate chemotherapy group (38). This study failed to accrue the planned number of patients (284 of the planned 660) and therefore remains inconclusive. There is no evidence to support the use of carboplatin in patients who are ineligible for cisplatin NAC or AC; in this case, clinical trial or surveillance in absence of clinical trial options may be the best next step (39).

The pattern of relapse in patients who failed RC differs from patients with regional metastasis who relapse after response to NAC. In the first group, 30% present with local recurrence (6), whereas in the second group three-fourth of patients experience relapse at site of response (40). The aforementioned facts and review provide reasonable rationale for surgery to consolidate chemotherapy (41). It is also worth to mention that the presence of nodal involvement doesn't preclude the construction of orthotopic neobladder, because the majority of recurrences after RC are distant and recurrences (even locally ones) do not often affect the functionality of the neobladder (42). The EAU guidelines do not, however, recommend orthotopic neobladder for N2 and N3 patients (6).

### Management of patients with inoperable locally advanced tumour and/or distant metastasis

#### First line chemotherapy

Approximately, one fifth of BCa present in the industrialized countries present with either inoperable or metastatic disease (41). In these patients, cisplatin-based combination chemotherapy is the standard of care when possible. After the introduction of effective chemotherapy, the median survival has improved from 3–6 months to more than 1 year (43). The initial response rate using different regimens of first line cisplatin-based combination chemotherapy (MVAC, GC, HD-MVAC with G-CSF) is approximately 40–70% and the median OS is about 14 months. However, the long term survival is poor and most patients experience disease progression at a median time of 8 months. The best response was noted in patients with good performance status, adequate renal function, complete response and lymph node metastasis compared to those harboring visceral metastasis (44). Indeed, approximately one fifth of patients with lymph node only disease achieved 5-year DFS (45,46). Advance patient age, medical comorbidities, poor performance status and renal impairment are not uncommon in this subset of patients and they do not only prevent proper and full delivery of chemotherapy



regimens but are also associated with poor outcome (9,46). Actually, up to 50% of patients are unfit for cisplatin-based chemotherapy (47). For these patients options include a carboplatin-based regimen such as carboplatin plus gemcitabine or carboplatin, gemcitabine, plus paclitaxel or non-platinum based combinations i.e., paclitaxel plus gemcitabine (39). Gemcitabine plus carboplatin is the preferred regimen because of the lower rate of severe systemic toxicity (47). However, none of these regimens have any significant response rate. The promise lies in novel immunotherapeutics which seem to have substantial response rates regardless of the patient's renal function.

### Second line chemotherapy

Patients who experience disease progression or relapse after first-line chemotherapy carry dismal prognosis. In the US, a commonly used salvage systemic therapy is single agent taxane chemotherapy with OS of 6–9 months. A recent phase II trial, comparing combination taxane-containing combination chemotherapy versus single-agent taxane, in patients who failed prior platinum-based chemotherapy, showed improved OS in the combination group (48). In Europe, vinflunine is the standard in this disease state. It has survival advantage over best supportive care alone and is recommended by the ESMO and the EAU guidelines as the only approved second-line treatment (6,49). In this disease state too, immunotherapeutics will change therapeutic paradigms yielding better outcomes.

### Surgery as a consolidation therapy

Patients who respond to primary chemotherapy may benefit from surgical consolidation if the disease is limited and located in the regional lymph nodes or metastatic site/sites amenable to surgical removal (i.e., non-regional lymph node and/or some lung metastasis). The concept of metastasectomy in urothelial carcinoma was first described in the early 1980s, when Cowles *et al.* reported long-term survival (median length of 5 years) for six patients who underwent wedge resection for solitary pulmonary metastasis. After more than one decade, multiple reports started to demonstrate the suggested benefits of surgical excision of metastatic lesions as part of a multimodality approach (50). In the age of immunotherapeutics, reduction of tumor burden may become even more important.

Harry and colleagues assessed the impact of post-chemotherapy surgery in 80 patients with unresectable

(T4bNxM0) or inoperable tumor with extensive pelvic and/or retroperitoneal lymph node metastasis (T3 to 4, N2 to 3, M0 to 1). They found that 32 patients who had inoperable disease became resectable after chemotherapy with half of them having full resection of residual disease. About one third of cases who achieved complete response to chemotherapy and surgery survived up to 5 years. Patient who had complete response to chemotherapy benefitted most from post-chemotherapy surgery (51). In a retrospective study, Dodd *et al.* founded that 30 (60%) patients achieved complete response to chemotherapy and surgery, of which 10 (33%) remained alive at 5 years. Patients with unresectable tumor and regional lymph node involvement fared better than patients with visceral metastasis (52). Miller *et al.* also had reported on 55 patients with 55% overall complete response rate. They also found that patients with visceral metastasis had worse outcome (53). Siefker-Radtke and colleagues reported on 31 patients with 30 undergoing complete resection of metastatic sites; lung lesions were the most commonly resected site follow by distant lymph nodes. The median survival and 5-year OS from time of metastasectomy were 23 months and 33%, respectively (54). A multicenter experience from Germany reported on 44 patients with metastatic urothelial carcinoma who underwent metastasectomy as part of multimodality treatment (systemic chemotherapy was administered in 80% before and/or after surgery). Retroperitoneal lymph nodes, distant lymph nodes, lung, bone, adrenal, brain, small intestine and skin were the resected metastatic sites in descending order. Median CSS and PFS after surgery were 34 and 15 months, respectively. Lehmann *et al.* concluded that cure is possible, long-term control can be achieved and surgery should be part of a multimodality approach (50). Abe *et al.* reported on 48 patients with metastatic BCa who received first-line chemotherapy with 20 patients undergoing additionally either metastasectomy (lobectomy n=7; lymphadenectomy n=3; and local recurrence surgery n=2) or second line chemotherapy. They found that the number of chemotherapy cycles (five or more), resection of metastases, and site of metastasis (absence of local recurrence, bone or liver recurrence) were independently associated with prolonged survival (55). Taken together, we believe that metastasectomy, in selected patients, may be attempted in a shared decision making process with the patient. At this time, it seems that lymph node and lung are the best sites and that a complete response to chemotherapy improves the odds of benefiting from the surgery; performance status is certainly a key criteria.

### Non-regional lymph node resection (metastasectomy)

According to TNM classification, lymph node involvement above the bifurcation of common iliac arteries is classified as distant metastasis (56). For patients with lymph node metastasis above true pelvis (without synchronous visceral metastasis), upfront chemotherapy followed by consolidation surgery in patients with good response is becoming an accepted strategy. Sweeney *et al.* reported on 11 patients with non-regional lymph node metastasis without synchronous visceral involvement who underwent bilateral retroperitoneal lymph node dissection (RPLND) as a consolidation therapy after major response to chemotherapy; 7 out of 11 patients underwent metastasectomy simultaneously with RC. The median RFS was 7 months and the 4-year DSS rate was 36%. Based on their results, they concluded that RPLND is safe and potentially curative, especially in patients with no more than two lymph nodes with viable tumor after chemotherapy (57). Another series included 14 patients with supra-regional (para-aortic and para-caval) lymph node metastasis; all patients underwent four cycles of cisplatin-based combination chemotherapy followed by RC with a complete pelvic and retroperitoneal lymphadenectomy. They found that one fourth of patients survived 5 years using this approach (56). Although these series are small and consist of well-selected patients, one can appreciate the role of post-chemotherapy surgery. The challenge will be to choose the right patient and to balance complications with survival outcomes in harmony with patients' wishes.

### Pulmonary metastasectomy

A study from Japan assessed the factors associated with prolonged survival in 18 patients with urothelial carcinoma who underwent pulmonary metastasectomy for limited metastatic sites/sites. They identified solitary metastasis as a factor associated with long-term survival; 5-year survival was 85% compared to 20% for patients with multiple metastasis ( $P < 0.05$ ). Complete resection was possible in 16 patients with no operative mortality. The cumulative 5-year OS in this series was 47% (58).

The aforementioned overview supports the concept that resection of limited metastatic deposits is feasible, safe and may be beneficial. However, solid evidence is lacking and recommendations cannot be made since the cohorts are too heterogeneous and small with retrospective study design.

### Refractory metastatic disease

A phase II trial enrolled 70 patients with refractory metastatic BCa (not responding to MVAC chemotherapy) to assess the outcome of complete surgical resection of metastatic sites. They found that the median survival was 7 months with no survival advantage for metastasectomy regardless of the site of metastasis. An advantage was noted in the quality of life of patients who had symptomatic metastasis but not in those who harbored asymptomatic disease who actually, in turn, complained from reduced sense of well-being after the surgery (59).

### RC as sole therapy

Perioperative complications and outcome were evaluated in a series of 20 consecutive T4 patients who were subjected to primary RC. In only one patient complete resection was not accomplished (macroscopic soft tissue margin) and three patients had microscopic soft tissue margins on histopathological examination. Half of the patients died within a mean interval of 7 months after surgery. The authors concluded that RC is technically possible with acceptable perioperative morbidity. Their rationale was that NAC would delay delivery of definitive local therapy to a point where local growth may make the tumour unresectable (60). However, the sample size was small and the follow up was too short to draw any significant conclusion. In addition, their rationale has been refuted, as cisplatin-based combination chemotherapy is effective and may even downstage the tumour (32). Moreover, these patients are most likely to benefit from systemic therapy and are most likely to be administrable in the neoadjuvant setting (61).

### Salvage RC

Salvage RC is recommended for tumour recurrence after bladder-sparing approaches (6). It is estimated that between 25–45% of patients who initially select multimodality bladder-sparing therapy ultimately undergo salvage RC (62). Type of bladder preserving approach, pathological tumor stage and lymph status remain the strongest prognostic factors for survival outcomes after salvage RC (18,63,64). Salvage RC outcomes after partial cystectomy were evaluated in 72 patients with a median follow-up time of 10.9 year. Bruins and colleagues reported that extravesical

extension and lymph node metastasis were independently associated with disease recurrence and only 22% of those patients were salvaged by surgery after 5 years compared to 36% for patients who underwent immediate RC from the baseline cohort of 2,218 patients (65). Salvage RC was found to be associated with more complication rate than immediate RC. When complications were stratified into perioperative (within 90 days) and delayed, the immediate RC group had significantly higher cardiovascular complications (myocardial infarction, deep vein thrombosis, pulmonary embolism and blood transfusion) than the salvage RC group who had higher rates of wound infection, fascial dehiscence, anastomotic stricture and stomal revision (64).

### Palliative cystectomy

Patients with bladder tumour fixed to pelvic or abdominal wall (pT4b) and those with intractable bleeding may suffer from severe symptoms that necessitate intervention. Due to its high morbidity, surgery is not the first option and should be taken into consideration after failure of less invasive options such as palliative radiotherapy as the cancer-related life expectancy of these patients is very limited (6).

### Conclusions

BCa is a chemosensitive tumour and chemotherapy is the mainstay of treatment for metastatic disease state. However, this is rarely curative and most patients succumb eventually to their disease. There has been no major advance in the management of these patients since the introduction of cisplatin-based combination chemotherapy. Indeed, the 5-year survival for metastatic BCa has not improved over the last decades. Therefore, management of metastatic BCa represent a great challenge regarding accurate clinical staging, risk stratification and cancer control requiring new treatment strategies.

In non-metastatic disease, RC is the standard therapy for improving survival. The role of PLND is still today, especially in high-risk patients, an essential part of the procedure. What remains to be addressed is the extent of lymph node dissection and the optimal candidates for perioperative chemotherapy.

In the metastatic disease state, surgery may be beneficial as a part of a multimodality approach resulting in long term survival in selected patients. The advantage appears to be in patients with complete or major response to chemotherapy and those who have metastasis in site/sites that are

amenable to surgical resection, especially non-pelvic lymph nodes and lung metastasis. However, the evidence for RC and/or metastasectomy remains limited requiring larger, multicentre collaborations with homogenous patient population. Prospective randomized clinical trials and validated nomograms that incorporate molecular markers and/or quality of surgery to predict disease outcome and to balance risk distribution may help further refine evidence creation in this heterogeneous disease state.

With the advent of immunotherapeutics in urothelial carcinoma, we are at the beginning to live through a time with a radical change awaiting us in the management of micro-and macro-metastatic disease. We foresee here a radical change in the role of surgery in metastatic setting. There is no doubt that we need to do better in locally advanced and metastatic BCa and we will!

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