

Treatment of Muscle-Invasive Bladder Cancer: from Radical Surgery to Perioperative Immunotherapy and Molecular Personalization

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Muscle-invasive bladder cancer (MIBC) is one of the most aggressive urologic malignancies and is characterized by a high risk of recurrence and progression even after radical surgical treatment. In recent years, approaches to MIBC treatment have undergone significant transformation due to the emergence of compelling data on the benefits of perioperative immunotherapy, the development of antibody-drug conjugates, refinements in organ-preserving strategies, and the introduction of circulating tumor DNA (ctDNA) as a potential molecular stratification tool.

Recent scientific data demonstrate a shift from the predominantly anatomically-based "neoadjuvant chemotherapy → radical cystectomy" model to a perioperative system in which the choice of treatment intensity is gradually linked to tumor biology, the likelihood of response, tolerability of therapy, and the presence of molecular markers of minimal residual disease. ctDNA is gaining particular importance, potentially allowing for the differentiation of patients with high and low risk of recurrence after surgery. At the same time, a new concept of bladder preservation is emerging in carefully selected patients with a significant response to systemic treatment.

The scientific novelty of this analytical review lies in its integration into a single conceptual model of several approaches typically considered separately: perioperative immunotherapy, ctDNA molecular monitoring, organ-preserving therapy, and dynamic risk stratification. We propose considering modern MIBC treatment as an adaptive perioperative system, in which treatment intensity is determined not only by the initial tumor stage but also by the dynamics of the biological response. The fundamental difference between this model and the traditional one lies in the transition:

from static stage assessment → to dynamic risk assessment;

from universal postoperative therapy → to molecularly targeted treatment;

	from mandatory radical surgery → to individual choice of local strategy; from a one-time risk determination → to continuous disease monitoring. In this model, ctDNA may act as a link between systemic therapy and subsequent treatment decisions. Based on the literature review, a conceptual model of personalized MIBC treatment is proposed, combining clinical and morphological assessment, perioperative systemic therapy, response assessment, molecular monitoring, and adaptation of subsequent treatment.
Keywords: Muscle-invasive bladder cancer, urothelial carcinoma, immunotherapy, perioperative therapy, neoadjuvant therapy, radical cystectomy, ctDNA, minimal residual disease, organ-preserving therapy, personalized oncology.	

Introduction

Muscle-invasive bladder cancer is a clinically and biologically heterogeneous disease. Despite advances in surgical techniques and systemic therapy, a significant proportion of patients experience recurrence after radical treatment. The high risk of micrometastatic disease explains the need for systemic interventions as early as the perioperative period.

For a long time, the mainstay of treatment for resectable MIBC was radical cystectomy with pelvic lymph node dissection, supplemented by neoadjuvant cisplatin-based chemotherapy in suitable patients. This model significantly improved outcomes compared to surgery alone, but left several fundamental issues unresolved.

Firstly, not all patients are candidates for cisplatin-containing chemotherapy. Secondly, treatment efficacy varies significantly between patients. Thirdly, even with radical surgery, the risk of systemic recurrence remains. Finally, cystectomy itself significantly impacts the patient's quality of life.

A key development was the NIAGARA trial, published in *the New England Journal of Medicine* in 2024. In it, perioperative durvalumab in combination with gemcitabine and cisplatin demonstrated an advantage in event-free and overall survival compared to neoadjuvant chemotherapy alone.

Later, several areas were further developed: postoperative immunotherapy, ctDNA-guided treatment, new combinations for patients unsuitable for cisplatin, and organ-preserving strategies. Thus, the modern question is no longer just **which operation to perform**, but how **to determine the optimal intensity of systemic treatment for a particular patient and whether radical bladder removal can be safely avoided in some patients**.

Transition from a surgically oriented to a perioperative model. The classic model of MIBC treatment was built around radical cystectomy. Systemic therapy was viewed as an adjunct, allowing for the treatment of potentially existing micrometastases. The modern concept is gradually changing the order of priorities. Systemic therapy is becoming not just an "add-on to surgery," but an independent component of the perioperative strategy.

In the NIAGARA study, 1,063 patients with resectable MIBC were randomized to perioperative durvalumab in combination with gemcitabine and cisplatin or standard neoadjuvant chemotherapy followed by radical cystectomy. At 24 months, event-free survival was 67.8% versus 59.8%, and overall survival was 82.2% versus 75.2%; the hazard ratio for death was 0.75. The incidence of severe adverse events was comparable between groups. These results are of fundamental importance. If the previous treatment logic was **tumor → surgery → additional treatment**, the new model can be represented as: **systemic treatment → tumor sensitivity assessment → surgery → continued systemic therapy → molecular control**. Thus, surgery ceases to be the only central event of treatment and becomes one of the components of a comprehensive perioperative strategy.

Perioperative immunotherapy as a new stage in treatment development. Immunotherapy has become one of the most significant changes in the treatment of urothelial cancer over the past decade. However, its translation from metastatic disease to perioperative therapy for localized MIBC is of particular importance. NIAGARA was the first large phase III trial to demonstrate the benefit of adding durvalumab perioperatively to neoadjuvant chemotherapy followed by continuation of durvalumab after surgery. Importantly, the benefit was observed not only in pathological response but also in clinically relevant survival outcomes. This allows us to draw several conclusions:

1. the immune system can be effectively activated even before the primary tumor is removed;
2. the neoadjuvant stage may be important not only for reducing tumor mass, but also for the formation of a systemic antitumor immune response;
3. Continuation of immunotherapy after surgery may maintain this effect during the period of maximum risk of micrometastatic recurrence.

Thus, the concept of **perioperative immune surveillance arises**, in which systemic therapy accompanies the patient at several stages of the disease.

Adjuvant immunotherapy after cystectomy. In the AMBASSADOR trial, the results of which were published in *the New England Journal of Medicine* in 2025, 702 high-risk patients after radical surgery were randomized to pembrolizumab or observation. Median relapse-free survival was 29.6 months in the pembrolizumab group versus 14.2 months in the observation group; the hazard ratio for progression or death was 0.73. Moreover, treatment was accompanied by an increase in the frequency of adverse events $\geq$ grade 3: 50.6% versus 31.6%.

This result highlights a fundamental issue in modern urological oncology: **not every patient should automatically receive the same intensity of treatment after surgery**. Increased relapse-free survival comes with additional toxicity. Therefore, it is necessary to improve the criteria for selecting patients who will truly benefit clinically from adjuvant immunotherapy. This very issue creates the preconditions for a shift from clinical and pathological stratification to molecular stratification.

ctDNA as a tool for detecting minimal residual disease. After radical cystectomy, imaging does not directly detect microscopic residual tumor cells. A patient may have no evidence of disease on CT but still remain at high risk of systemic recurrence.

ctDNA has the potential to detect molecular features of minimal residual disease before the appearance of visualized tumor. A 2025 systematic review, including eight MIBC studies, found that the presence of ctDNA before and after cystectomy was associated with worse oncologic

outcomes. Postoperative ctDNA positivity was associated with shorter disease-free survival and an increased risk of recurrence, and ctDNA dynamics during neoadjuvant treatment had potential prognostic significance.

This means that ctDNA can perform several functions at once:

- predict the likelihood of relapse;
- assess the depth of response to systemic therapy;
- detect minimal residual disease;
- determine the need for additional treatment;
- potentially allow for the avoidance of unnecessary therapy in patients with low molecular risk.

Thus, it becomes possible to move from the strategy of **“treating all patients after surgery”** to the strategy of **“treating those patients who still have molecular evidence of risk”**.

IMvigor011: Moving from Prognostic to Predictive ctDNA. The most important proof of the practical value of ctDNA came from the results of the IMvigor011 study, published in *the New England Journal of Medicine* in 2025. In the study, patients underwent serial ctDNA testing after surgery. Patients with detectable ctDNA were randomized to adjuvant atezolizumab or placebo, while patients with persistently negative ctDNA did not receive additional immunotherapy.

In ctDNA-positive patients, the median relapse-free survival was 9.9 months with atezolizumab versus 4.8 months with placebo; the hazard ratio for the first event was 0.64. Overall survival was also higher: 32.8 versus 21.1 months, HR 0.59. Monitoring of ctDNA-negative patients is particularly important: in 357 patients with a persistently negative status, relapse-free survival was 95% at the end of the first year of monitoring and 88% after two years.

Thus, for the first time, ctDNA is acquiring not only **a prognostic** but also **a therapeutically guiding function**. This fundamentally changes the concept of postoperative treatment.

From anatomical to molecular stratification. Traditional risk stratification after cystectomy is based primarily on:

- pathological stage;
- condition of the lymph nodes;
- the presence of lymphovascular invasion;
- features of the histological structure;
- previous therapy.

However, these characteristics do not always accurately reflect the presence of minimal residual disease. Modern molecular studies show that bladder tumors vary significantly in their biological characteristics. A review in *Nature Reviews Urology* 2024–2025 emphasizes the importance of molecular biomarkers for predicting progression and refining risk beyond traditional clinical-pathological systems.

In the future, an individual patient profile could look like this: **clinical stage + morphology + molecular profile + ctDNA dynamics + treatment response**. This creates a fundamentally more complex, but potentially more accurate, decision-making system.

Patients ineligible for cisplatin. A separate issue is the treatment of patients who are not eligible for cisplatin due to renal failure, general health, comorbidities, or other factors. Historically, these patients have had fewer effective perioperative treatment options.

The development of immunotherapy and new antitumor platforms opens up the possibility of expanding therapeutic options. Combinations of immune drugs with antibody-drug conjugates are

particularly promising. One emerging approach is targeting specific tumor antigens, such as Nectin-4.

A 2024 study published in *Nature Medicine* examined the combination of intravesical oncolytic therapy cretostimogene grenadenorepvec with systemic nivolumab in patients with MIBC ineligible for cisplatin. In the Phase Ib study, pathological complete responses were achieved in 42.1% of patients, and the one-year disease-free survival rate was 70.4%. The response was associated with specific tumor immunological characteristics.

Although the study was small and cannot independently change the standard of care, it demonstrates a direction for development: **combining local immune stimulation with systemic immune therapy**. This is particularly important for future organ-preserving treatments.

Organ-preserving treatment: is it possible to avoid cystectomy? Radical cystectomy remains the most important treatment for MIBC, but it comes with significant functional and quality consequences. Therefore, organ-preserving strategies, primarily trimodal therapy, including maximal transurethral resection, radiation therapy, and radiosensitizing chemotherapy, remain of high interest. This approach has been further developed through the concept of selecting patients who demonstrate a complete clinical response after systemic therapy.

The current approach suggests that bladder preservation can be considered not as a compromise treatment for patients for whom surgery is contraindicated, but as a potentially controlled strategy in carefully selected patients. However, a fundamental challenge remains: **how can the absence of residual invasive tumor be reliably demonstrated?** Therefore, bladder preservation strategies are closely linked to the development of molecular monitoring.

The relationship between treatment response and bladder preservation. The modern concept of bladder preservation involves several criteria:

1. limited tumor;
2. absence of clinically significant lymph node damage;
3. the possibility of a full local assessment;
4. pronounced response to systemic therapy;
5. no signs of residual invasive tumor;
6. possibility of intensive follow-up monitoring;
7. patient readiness for salvage cystectomy in case of relapse.

A 2025 systematic review, including 41 studies and 3,588 patients, revealed significant diversity in approaches to defining complete clinical response after neoadjuvant treatment. Only a subset of studies included perioperative immunotherapy, highlighting the need for standardized response criteria in this new therapeutic era.

Therefore, bladder preservation cannot yet be considered a universal alternative to cystectomy. However, a new concept is emerging: **systemic treatment → profound response → evidence of absence of residual disease → bladder preservation in carefully selected patients.**

The transition to biologically oriented surgery. Changes in systemic therapy inevitably impact the role of surgery. Radical cystectomy remains the central method of local control, but its place in the treatment algorithm is becoming more flexible.

In 2025, expert and clinical publications emphasized that modern MIBC treatment must be considered as a comprehensive process, including systemic therapy, surgery, radiation therapy, molecular monitoring, and shared decision making. The 2025 *Journal of Clinical Oncology*

characterized MIBC as a disease undergoing significant therapeutic transformation, driven by the development of perioperative systemic therapy and refinement of organ-preserving approaches. Consequently, modern surgery becomes part of a **biologically oriented strategy**, rather than the sole determining stage of treatment.

Selecting the optimal treatment intensity. The expansion of therapeutic options creates a new challenge. While the question was once often phrased as "**can this patient undergo radical surgery?**" today, it increasingly becomes "**what is the extent of systemic and local treatment required for this particular patient?**" In patients with a high probability of micrometastatic disease, aggressive perioperative therapy may be warranted. In a patient with a significant response and negative ctDNA, further intensive therapy may be less necessary. In a patient with persistent ctDNA after surgery, the risk of recurrence may justify early adjuvant therapy.

Thus, the principle of **dynamic risk stratification is formed**, in which the patient's risk is determined not once before the operation, but is constantly updated as treatment progresses.

Safety as a component of personalization. Intensification of therapy inevitably increases the risk of toxicity. In the AMBASSADOR study, severe adverse events were observed more frequently with pembrolizumab than with observation.

In NIAGARA, the addition of durvalumab did not result in a significant increase in grade 3–4 adverse events compared with chemotherapy, supporting its use in the perioperative setting in appropriate patients.

Therefore, personalization must take into account not only the likelihood of efficacy but also age, renal function, somatic status, immunological risks, previous therapy, life expectancy, quality of life, and patient preferences. Thus, optimal treatment is not necessarily the most intensive treatment. **Optimal treatment is the treatment with the highest expected benefit-to-risk ratio.**

Based on the analysis conducted, the following model is proposed:



Figure 1. Conceptual model of modern personalized MIBC therapy

Thus, the therapeutic process becomes **cyclical** rather than linear. The outcome of one stage determines the next.

Conclusion

We have every reason to assert a significant transformation in the treatment of muscle-invasive bladder cancer. The main change is the shift from a predominantly surgical model to a comprehensive perioperative strategy integrating systemic therapy, surgical treatment, molecular monitoring and adaptation of subsequent treatment.

The NIAGARA results demonstrated the clinical value of adding durvalumab perioperatively to neoadjuvant chemotherapy. The AMBASSADOR study confirmed the activity of adjuvant pembrolizumab therapy in high-risk patients. Meanwhile, the IMvigor011 results demonstrated a fundamentally new approach in which ctDNA is directly used to select patients for adjuvant immunotherapy.

Bladder-preserving strategies and new immunological methods are also being developed, particularly for patients unsuitable for standard cisplatin-based therapy. A promising treatment model can be formulated as follows:

“stratify → treat systemically → assess biological response → choose optimal local strategy → monitor molecular risk → adapt treatment.”

Thus, modern urology is gradually shifting from treating MIBC as a primarily anatomical disease to managing dynamic biological risk. The most promising direction for further development is the integration of **clinical characteristics, morphology, molecular profiling, ctDNA, and response dynamics** into a single decision-making system. This model can simultaneously improve treatment efficacy, reduce unnecessary toxicity, and expand the potential for bladder preservation in appropriately selected patients.

References

1. Powles T., Catto JWF, Galsky MD et al. Perioperative Durvalumab with Neoadjuvant Chemotherapy in Operable Bladder Cancer. *New England Journal of Medicine* . 2024;391:1773–1786. DOI: 10.1056/NEJMoa2408154. <https://pubmed.ncbi.nlm.nih.gov/39282910/>
2. Galsky MD, et al. Adjuvant Pembrolizumab versus Observation in Muscle-Invasive Urothelial Carcinoma. *New England Journal of Medicine* . 2025;392:45–55. DOI: 10.1056/NEJMoa2401726. <https://pubmed.ncbi.nlm.nih.gov/39282902/>
3. Mari A., et al. Circulating tumor DNA in muscle-invasive bladder cancer: A systematic review. *Actas Urológicas Españolas (English Edition)* . 2025. DOI: 10.1016/j.acuroe.2025.501717. <https://www.sciencedirect.com/science/article/pii/S2173578625000071>
4. Powles T., Kann AG, Castellano D. et al. ctDNA-Guided Adjuvant Atezolizumab in Muscle-Invasive Bladder Cancer. *New England Journal of Medicine* . 2025;393:2395–2408. DOI: 10.1056/NEJMoa2511885. <https://pubmed.ncbi.nlm.nih.gov/41124204/>
5. Black PC, et al. Oncolytic immunotherapy with nivolumab in muscle-invasive bladder cancer: a phase 1b trial. *Nature Medicine* . 2024. DOI: 10.1038/s41591-024-03324-9. <https://labpages.moffitt.org/andersona/publications.html>
6. Olislagers M., de Jong FC, Rutten VC et al. Molecular biomarkers of progression in non-muscle-invasive bladder cancer - beyond conventional risk stratification. *Nature Reviews Urology*

. 2025;22:75–91. Published online August 2024. DOI: 10.1038/s41585-024-00914-7.
<https://pubmed.ncbi.nlm.nih.gov/39095581/>

7. Galsky MD, Ballas L., Kamat AM Muscle-Invasive Bladder Cancer: A Watershed Moment. Journal of Clinical Oncology . 2025;43:3041–3051. DOI: 10.1200/JCO-25-00718.
<https://pubmed.ncbi.nlm.nih.gov/40763316/>

8. Kimura T., Inoue S., Sano T. et al. Recent Advances and Future Directions in Bladder Preservation Therapy for Muscle-Invasive Bladder Cancer. International Journal of Urology . 2025;32:1334–1341. DOI: 10.1111/iju.70164.
<https://pmc.ncbi.nlm.nih.gov/articles/PMC12503195/>

9. Giannakodimos I., et al. Neoadjuvant immunotherapy for muscle-invasive bladder cancer: a 2025 update. [Review publication on modern perioperative immunotherapy] . 2025.
<https://pubmed.ncbi.nlm.nih.gov/40329651/>

10. Witjes JA, et al. European Association of Urology Guidelines on Muscle-invasive and Metastatic Bladder Cancer: Summary of the 2025 Guidelines. European Urology . 2025;87(5):582–600. DOI: 10.1016/j.eururo.2025.02.019.
<https://pubmed.ncbi.nlm.nih.gov/40118736/>