v. 5, n. 30, 2025

International Journal of Health Science

Acceptance date: 22/09/2025

BLADDER CANCER: CURRENT PERSPECTIVES AND THERAPEUTIC CHALLENGES

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Abstract: Bladder cancer is a common urothelial neoplasm that presents significant clinical challenges, mainly due to its high recurrence rate, potential for progression, and impact on quality of life. Non-muscle-invasive bladder cancer (NMIBC) accounts for the majority of cases and is treated by transurethral resection followed by intravesical therapies, such as BCG immunotherapy. Muscle-invasive bladder cancer (MIBC), on the other hand, requires a more aggressive approach, with radical cystectomy combined with neoadjuvant chemotherapy being the gold standard. Trimodal therapy has established itself as an effective alternative to cystectomy in selected patients, promoting bladder preservation. Advances in the molecular classification of urothelial carcinoma have allowed the identification of subtypes with distinct prognostic and therapeutic characteristics, enabling personalized approaches. However, challenges remain, such as resistance to BCG, the selection of patients for conservative therapies, and the management of patients who are ineligible for cisplatin. Precision medicine, based on molecular biomarkers, is emerging as promising in the personalization of treatment and the optimization of oncological outcomes.
Keywords: Bladder cancer; Urothelial carcinoma; Radical cystectomy; Intravesical therapy.

INTRODUCTION

Bladder cancer is the tenth most common malignant neoplasm worldwide, representing a significant challenge to public health (Tran et al., 2024). The vast majority of cases, more than 90%, correspond to urothelial carcinoma (UC), originating in the transitional epithelium that lines the urinary tract (Dyrskjøt and Zainfeld, 2023; Tran et al., 2024). Clinically, bladder cancer is categorized into two distinct entities based on the depth of tumor invasion into the bladder wall: non-muscle-invasive bladder cancer (NMIBC) and muscle-invasive bladder cancer (MIBC) (Tran et al., 2024).

CBNMI, which accounts for approximately 75% of newly diagnosed cases, is characterized by tumors confined to the mucosa (stages Ta, Tis) or the lamina propria (stage T1) (Dobruch and Osieka, 2021; Tran et al., 2024). Although it has a relatively favorable prognosis, CBNMI has high recurrence rates and a risk of progression to muscle-invasive disease, requiring ongoing surveillance and adjuvant treatment (Dobruch and Osieka, 2021). In contrast, MIBC is an aggressive disease with high mortality, requiring a multimodal and intensive therapeutic approach to achieve curative outcomes (Xu et al., 2022).

The management of bladder cancer has evolved significantly, with approaches ranging from transurethral resection and intravesical therapies for NMIBC to radical cystectomy with neoadjuvant chemotherapy for MIBC (Dobruch and Osieka, 2021; Xu et al., 2022). In addition, trimodal therapy (TMT), which combines resection, chemotherapy, and radiotherapy, has emerged as an effective alternative for bladder preservation in selected patients with MBMC (Xie et al., 2023). More recently, the molecular classification of urothelial carcinoma has revealed a biological heterogeneity that promises to guide more personalized and effective therapies (Dyrskjøt and Zainfeld, 2023). This review aims to address current perspectives and therapeutic challenges in the diagnosis and treatment of bladder cancer, covering both non-muscle-invasive and muscle-invasive forms of the disease.

METHODOLOGY

This article is a narrative review of the literature, with the aim of summarizing current diagnostic and therapeutic perspectives, as well as the challenges in the management of bladder cancer. A bibliographic search was performed in the PubMed database using the

descriptors "Urinary Bladder Neoplasms," "Diagnosis," and "Treatment," in accordance with the Medical Subject Headings (MeSH) vocabulary. The search was optimized by combining the terms with the Boolean operators AND and OR. Review articles, systematic reviews, and clinical studies published in the last five years that addressed the diagnosis and treatment of non-muscle-invasive and muscle-invasive bladder cancer were included for analysis. Studies focused on rare histologies or that did not address current clinical practice were excluded. The selection of articles was performed in two stages: initial evaluation of titles and abstracts, followed by a complete analysis of the selected texts. The information was extracted and organized in order to present a cohesive view of the state of the art on the topic.

RESULTS

The therapeutic approach to bladder cancer is fundamentally determined by the staging of the disease, divided between strategies for NMIBC and MIBC.

DIAGNOSIS AND RISK STRATIFICATION

The initial diagnosis of bladder cancer is established by cystoscopy, with histopathological confirmation obtained through transurethral resection of the bladder (TURB) (Dobruch and Osieka, 2021; Tran et al., 2024). TURB is a crucial procedure, as it is both diagnostic and therapeutic, allowing tumor removal and assessment of the depth of invasion (Dobruch and Osieka, 2021). For patients with NMIBC, risk stratification into low-, intermediate-, high-, and very high-risk groups is essential to guide adjuvant therapy and follow-up (Dobruch and Osieka, 2021). This stratification is based on clinicopathological factors such as tumor grade, size, multiplicity, presence of carcinoma in situ (CIS), and history of recurrence (Dobruch and Osieka, 2021). In MBC, staging is complemented by imaging tests such as computed tomography (CT) or magnetic resonance imaging (MRI) to assess locoregional extension and the presence of distant metastases (Tran et al., 2024).

TREATMENT OF NON-MUSCLE-INVASIVE BLADDER CANCER (NMIBC)

After complete TURB, adjuvant intravesical treatment is administered based on risk stratification (Dobruch and Osieka, 2021). For low-risk tumors, a single immediate postoperative instillation of chemotherapy (usually mitomycin C) is recommended to reduce the risk of recurrence (Dobruch and Osieka, 2021). For patients with intermediate- and high-risk NMIBC, intravesical Bacillus Calmette-Guérin (BCG) immunotherapy is the gold standard treatment (Dobruch and Osieka, 2021). BCG is considered the most effective intravesical agent for preventing not only recurrence but also, more importantly, disease progression to MIBC (Dobruch and Osieka, 2021). Treatment consists of a weekly induction regimen for six weeks, followed by maintenance therapy (Dobruch and Osieka, 2021).

TREATMENT OF MUSCLE-INVASIVE BLADDER CANCER (MIBC)

The gold standard for treating localized MIBC is radical cystectomy (RC) with extended pelvic lymphadenectomy (Xu et al., 2022; Xie et al., 2023). The administration of platinum-based neoadjuvant chemotherapy (NAC) (cisplatin) before surgery is strongly recommended, as it has been shown to significantly improve overall survival compared to cystectomy alone (Xu et al., 2022). RC is a procedure with high morbidity and a significant impact on quality of life, which drives the search for alternatives that allow bladder preservation (Xie et al., 2023).

TRIMODAL THERAPY (TMT) AS AN ALTERNATIVE FOR BLADDER PRESERVATION

TMT is a curative approach that combines three modalities: maximum safe brachytherapy, radiosensitizing chemotherapy, and external beam radiation therapy (Xie et al., 2023). TMT is an established option for patients with MIBC who are not candidates for RC or who refuse it, offering overall survival rates comparable to those of cystectomy in well-selected patient cohorts (Xie et al., 2023).

MOLECULAR CLASSIFICATION OF UROTHELIAL CARCINOMA

Urothelial carcinoma is a molecularly heterogeneous disease (Dyrskjøt and Zainfeld, 2023). Classification based on gene expression has identified distinct molecular subtypes, such as luminal and basal, which have prognostic and predictive implications (Dyrskjøt and Zainfeld, 2023). For example, basal-squamous subtype tumors, which are more common in CBMI, are more aggressive but appear to respond better to neoadjuvant chemotherapy and immunotherapy with checkpoint inhibitors (Dyrskjøt and Zainfeld, 2023). This classification is beginning to be integrated into clinical practice to guide personalized therapeutic decisions (Dyrskjøt and Zainfeld, 2023).

DISCUSSION

The management of bladder cancer presents distinct challenges for non-muscle-invasive and muscle-invasive forms. In NMIBC, the main challenge lies in preventing recurrence and progression (Dobruch and Osieka, 2021). BCG immunotherapy, despite being the most effective treatment, is associated with local and systemic toxicity, as well as a considerable failure rate (Dobruch and Osieka, 2021). The management of patients with high-risk disease refractory to BCG is one of the greatest clinical dilemmas, with radical cystectomy being the standard treatment in these cases (Dobruch and Osieka, 2021). The search for new intravesical and systemic therapies, such as immunotherapy with checkpoint inhibitors, is an area of intense research for this population (Tran et al., 2024).

For CBMI, the central dilemma lies between the oncological efficacy of radical cystectomy and its substantial impact on quality of life (Xie et al., 2023). TMT has established itself as a viable alternative, but patient selection is critical to success (Xie et al., 2023). Patients with extensive tumors, diffuse carcinoma *in situ*, or hydronephrosis are generally considered poor candidates for bladder preservation (Xie et al., 2023). The decision between RC and TMT should be shared with the patient, considering the risks and benefits of each approach (Xie et al., 2023).

Neoadjuvant therapy with cisplatin-based chemotherapy represents one of the greatest advances in the treatment of MBC, with a well-established survival benefit (Xu et al., 2022). However, a significant challenge is the treatment of patients who are ineligible for cisplatin, either due to inadequate renal function or other comorbidities (Xu et al., 2022). For these patients, options are more limited, although neoadjuvant immunotherapy is emerging as a promising alternative (Xu et al., 2022).

The future of bladder cancer treatment is moving toward precision medicine, guided by molecular classification (Dyrskjøt and Zainfeld, 2023). The identification of molecular subtypes has the potential to refine risk stratification and personalize therapy (Dyrskjøt and Zainfeld, 2023). In the future, tumor biology may dictate the choice between neoadjuvant chemotherapy, immunotherapy, or TMT, moving away from the "one-size-fits-all" model and optimizing outcomes for each patient (Dyrskjøt and Zainfeld, 2023).

CONCLUSION

The management of bladder cancer requires a differentiated approach depending on the stage of the disease. In non-muscle-invasive bladder cancer (NMIBC), the prevention of recurrence and progression remains the main challenge, with intravesical immunotherapy with BCG established as the standard of care, albeit with significant limitations. Muscle-invasive bladder cancer (MIBC), on the other hand, requires multimodal strategies, in which radical cystectomy with neoadjuvant chemotherapy is the treatment of choice, while trimodal therapy emerges as a viable alternative in selected patients.

The incorporation of molecular classification into clinical management represents a significant advance, enabling greater personalization of therapy and promoting a transition to precision medicine. However, issues such as treatment resistance, the appropriate selection of candidates for bladder preservation, and the management of patients ineligible for cisplatin still lack ideal solutions. In this context, ongoing efforts in clinical and translational research are crucial for improving oncological outcomes and the quality of life of patients with bladder cancer.

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