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MINIREVIEWS

Histologic subtypes of non-muscle invasive bladder cancer

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Abstract

The majority of bladder cancers (BCs) are non-muscle invasive BCs (NMIBCs) and show the morphology of a conventional urothelial carcinoma (UC). Aberrant morphology is rare but can be observed. The classification and characterization of histologic subtypes (HS) in UC in BC have mainly been described in muscle invasive bladder cancer (MIBC). However, the currently used classification is applied for invasive urothelial neoplasm and therefore, also valid for a subset of NMIBC. The standard transurethral diagnostic work-up misses the presence of HS in NMIBC in a considerable percentage of patients and the real prevalence is not known. HS in NMIBC are associated with an aggressive phenotype. Consequently, clinical guidelines categorize HS of NMIBC as "(very) high-risk" tumors and recommend offering radical cystectomy to these patients. Alternative strategies for bladder preservation can only be offered to highly selected patients and ideally within clinical trials. Novel treatment strategies and biomarkers have been established MIBC and NMIBC but have not been comprehensively investigated in the context of HS in NMIBC. Further evaluation prior to implementation into clinical practice is needed.

Key Words: Urothelial carcinoma; Non-muscle invasive bladder cancer; Muscle invasive bladder cancer; Histologic subtypes; Histologic variants

Core Tip: The currently used classification for histologic subtypes (HS) in urothelial carcinoma has mainly been described in muscle invasive bladder cancer. However, a subset of non-muscle invasive bladder cancer presents HS, and their presence is clinically relevant. In this minireview, we discuss the epidemiology, classification, characterization and the clinical relevance of HS in non-muscle invasive bladder cancer.

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INTRODUCTION

The majority (75%) of bladder cancers (BCs) are non-muscle invasive BCs (NMIBCs) and are confined to the mucosa or the submucosa. While most NMIBC show the morphology of conventional urothelial carcinoma (UC), aberrant morphology can be observed. These so-called histologic subtypes (HS) were first described in the literature in the 1990s in small case series. More recently, an increasing interest in the biological and clinical characteristics of HS has emerged. In the literature, HS are mainly investigated in radical cystectomy (RC) specimens from patients with muscle-invasive bladder cancer (MIBC). Only for selected specific HS, have aggressive features in NMIBC been identified. However, HS have raised the interest of scientists, urologists and oncologists due to emerging novel diagnostic and therapeutic options. The purpose of this mini-review is to summarize the current literature on HS in NMIBC. Further evaluation prior to implementation into clinical practice is needed.

HS IN NMIBC

Classification

According to the fifth and new edition of the 2022 World Health Organization (WHO) Classification, histologic characteristics are still considered the gold standard for the classification. Due to the recent considerable advances in understanding the genomic landscape of UC and definition of intrinsic molecular subtypes, their future potential clinical impact is acknowledged in the new 2022 WHO Classification. Regarding HS in UC, investigations have mainly been conducted in MIBC and a separate classification of HS in NMIBC has not been described. However, the classification still includes the category "invasive urothelial carcinoma", which includes a subset of NMIBC.

Table 1 indicates the current classification of tumors of the urinary tract. Further categories listed in this table, such as noninvasive urothelial neoplasms and nonurothelial tumors (metastatic, hematolymphoid, mesenchymal, neuroendocrine, and genetic syndrome-related tumors), are not further discussed in this article[1].

The real incidence of HS in NMIBC is unknown and is not comprehensively investigated in the literature. In cystectomy series, pure UC is present in two-thirds of the patients and is the most common histologic entity in BC. Cystectomy series of patients with NMIBC likely overestimate the incidence of HS because these are associated with more aggressive tumor characteristics and are more frequently treated with RC[2].

Accuracy of transurethral resection of the bladder tumor in detecting HS

NMIBC is treated by transurethral resection of the bladder tumor (TURBT) to confirm the diagnosis, define tumor grading, and ideally remove the entire tumor. Pathological evaluation of TURBT specimens has several limitations. In the context of this article, we are focusing on the diagnostic accuracy and potential limitations of TURBT in evaluating the presence of HS. Several studies have shown low concordance between the presence of HS in TURBT and RC[3]. By contrast, other retrospective studies have reported a relatively high rate of detecting HS in TURBT[4]. The reasons for these conflicting results are likely related to the heterogeneity of patient populations, resection techniques, and pathological work-up.

Another critical aspect is the missed diagnosis of HS in the initial pathological reporting, as shown by Kamat *et al*[5]. after reviewing specimens of 100 patients with micropapillary NMIBC. This last aspect is not only related to the experience of the pathologist in uropathology, as interobserver variability between experienced uropathologists is also a critical issue[6].

In summary, TURBT alone likely misses the presence of HS in NMIBC in a considerable percentage of patients, and a comprehensive investigation of this clinically relevant issue has not yet been published.

TREATMENT OPTIONS

According to the current American Urological Association and European Association of Urology guidelines, NMIBC with HS should be considered" (very) high-risk" tumors in the risk stratification for primary UC. This recommendation is based on the association of HS with more advanced TNM stage, worse outcomes, and increased risk of treatment failure after bladder-sparing therapy in T1 disease. Moreover, the risk of progression is significantly higher in patients with HS (16% after 1 year, 40% after 5 years) and therefore, clinical guidelines suggest offering primary RC in these patients[7]. Due to the diagnostic challenges and limitations, and considering the limited data, an assessment of prognostic differences among HS in NMIBC cannot be made.

Table 1 Classification of tumors of the urinary tract

Category	Features
Urothelial tumors	Invasive urothelial neoplasms: (1) Conventional urothelial carcinoma; (2) Urothelial carcinoma with squamous differentiation; (3) Urothelial carcinoma with glandular differentiation; (4) Urothelial carcinoma with trophoblastic differentiation; (5) Nested urothelial carcinoma; (6) Large nested urothelial carcinoma; (7) Tubular and microcystic urothelial carcinomas; (8) Micropapillary urothelial carcinoma; (9) Lymphoepithelioma-like urothelial carcinoma; (10) Plasmacytoid urothelial carcinoma; (11) Giant cell urothelial carcinoma; (12) Lipid-rich urothelial carcinoma; (13) Clear cell (glycogen-rich) urothelial carcinoma; (14) Sarcomatoid urothelial carcinoma; and (15) Poorly differentiated urothelial carcinoma Noninvasive urothelial neoplasms: (1) Urothelial papilloma; (2) Urothelial papilloma, inverted; (3) Papillary urothelial neoplasm of low malignant potential; (4) Inverted papillary urothelial neoplasm of low malignant potential; (5) Noninvasive papillary urothelial carcinoma, low grade; (6) Low-grade papillary urothelial carcinoma with an inverted growth pattern; (7) Noninvasive papillary urothelial carcinoma, high grade; (8) Noninvasive high-grade papillary urothelial carcinoma with an inverted growth pattern; and (9) Urothelial carcinoma in situ
Nonurothelial tumors	(1) Squamous cell neoplasms of the urinary tract; (2) Glandular neoplasms; (3) Adenocarcinomas; (4) Urachal and diverticular neoplasms; (5) Urethral neoplasms; and (6) Tumors of Mullerian type

Instillation therapy

In a retrospective series of 44 patients with micropapillary NMIBC treated with bacillus Calmette-Guérin (BCG), 67% of these patients experienced tumor progression, 22% developed metastasis, and two-thirds ended up with secondary RC [5]. Another retrospective series of 36 patients with micropapillary NMIBC, 21 of whom underwent primary conservative therapy (BCG, surveillance, deferred RC), showed a slightly lower tumor progression rate (10%), a similar rate of metastasis (19%), and a 5-year cancer-specific mortality of 25% (*vs* 17% in the subcohort undergoing early RC; $P = 0.8$)[8]. In 2015, Willis *et al*[9] analyzed 72 patients with micropapillary UC staged as cT1N0M0. Of the 40 patients who received primary BCG therapy, 75% had recurrence, 45% showed progression, and 35% developed metastasis. Five-year disease-specific survival was 60% (*vs* 100% in the subgroup with upfront RC; $P = 0.006$). In 2020, Prado *et al*[10] reviewed 347 patients with NMIBC (59 with HS, 288 with pure UC) who underwent intravesical treatment with BCG. Surprisingly, recurrence-free survival was greater in the HS group compared to the pure UC group (62.1% *vs* 38.0%; $P < 0.05$). The authors concluded that a selected subpopulation may be treated with BCG. However, these results were presented as an abstract in 2020 and a final publication is still pending.

More recently, a systematic review analyzed 16 studies from 2011 to 2020 on NMIBC with HS. According to their analysis, TURBT and BCG seem to be feasible in NMIBC with squamous and/or glandular differentiation in selected patients with low tumor burden and without risk factors. For most HS (*e.g.*, micropapillary, sarcomatoid, plasmacytoid, and nested variant), RC should be considered first-line therapy[11].

Novel treatment options and promising biomarkers

More recently, several novel intravesical treatments and regimens have been discovered and investigated for the treatment of NMIBC[12-14]. Moreover, systemic treatment with check-point inhibition is being tested with or without intravesical instillation therapies[15]. None of these investigations and trials have focused on the antitumor activity in NMIBC with HS. Therefore, these alternative strategies for bladder preservation should only be offered to highly selected patients and ideally within a clinical trial.

Novel biomarkers such as cell-free circulating tumor DNA (ctDNA) in serum or even urine have been discovered[15, 16]. They are thought to reflect the residual tumor more accurately compared to the current standard of care. This approach may be promising in some HS that have been associated with specific genomic alterations. For example, the plasmacytoid variant shows frequent somatic cadherin 1 loss-of-function mutations[17]. Whereas, large nested variant is fibroblast growth factor receptor 3-mutated[18]. Whether ctDNA allows exploitation of these genomic characteristics in specific HS and better reflect residual disease or tumor recurrence remains to be shown. However, more accurate monitoring of the tumor burden and clinical course may allow bladder preservation in such selected situations.

CONCLUSION

The presence of HS is underdiagnosed by TURBT in MIBC, while in NMIBC findings are not consistent. Upfront radical surgery should be offered to these patients whereas bladder preservation may be performed in selected cases or within clinical trials. Predictive models like the European Organization for Research and Treatment of Cancer risk tables should include HS in the future. Novel treatment strategies and biomarkers seem to be promising but require further evaluation before implementation into daily routine.

FOOTNOTES

Author contributions: Giudici N performed the majority of the writing and prepared the tables; Seiler R provided input and supervision in writing the paper; Both authors have read and approved the final manuscript.

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