



# Histological variants in non-muscle invasive bladder cancer

Philipp Baumeister<sup>1</sup>, Stefania Zamboni<sup>1,2</sup>, Agostino Mattei<sup>1</sup>, Alessandro Antonelli<sup>2</sup>, Claudio Simeone<sup>2</sup>, Livio Mordasini<sup>1</sup>, Carlo DiBona<sup>1</sup>, Marco Moschini<sup>1</sup>; on behalf of the EAU Young Academic Urologists—Urothelial Cancer Working party

<sup>1</sup>Klinik für Urologie, Luzerner Kantonsspital, Lucerne 6004, Switzerland; <sup>2</sup>Department of Urology, Spedali Civili di Brescia, Brescia 25123, Italy

**Contributions:** (I) Conception and design: P Baumeister, M Moschini; (II) Administrative support: A Mattei; (III) Provision of study materials or patients: P Baumeister, S Zamboni, L Mordasini, C DiBona, A Mattei; (IV) Collection and assembly of data: C DiBona; (V) Data analysis and interpretation: P Baumeister, M Moschini, S Zamboni; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

**Correspondence to:** Prof. Dr. med. Agostino Mattei. Klinik für Urologie, Kantonsspital Luzern, Luzern, Switzerland. Email: agostino.mattei@luks.ch.

**Abstract:** Several studies evaluated the role of histological variants on oncological outcomes after radical cystectomy (RC) and they were found significantly associated with worse recurrence and survival. Sparse data exists regarding the role variant histology in non-muscle invasive diseases: assessing their relationship with recurrence and progression is important to understand the most effective treatment and follow-up schedule. For these reasons, the aim of the present non-systematic review was to assess the literature on variant histology in non-muscle invasive bladder cancer (BCa). The diagnosis of presence variant histology at transurethral resection (TUR) specimens challenging for pathologists and several studies published in literature evaluated concordance between TUR and RC specimen with discordant results. These differences are probably related to diversity in collection of samples and pathological evaluation and underline the necessity to have good tissue-sample and a pathologic evaluation performed by expert and dedicated uropathologists. Treatment of BCa with variant histology shall include immediate RC in case of plasmacitoid, pure squamous, micropapillary and sarcomatoid variants. The neuroendocrine differentiation, therefore, showed chemosensitiveness, and RC preceded by neoadjuvant chemotherapy should be proposed. Intravesical instillations with Bacillus Calmette Guerin (BCG) can be suggested in very selected cases of nested and glandular variants.

**Keywords:** Bladder cancer (BCa); bladder tumor; NMIBC; histological variants; high-risk urothelial cancer

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## Introduction

Bladder cancer (BCa) is the second most common tumor of the urogenital system following prostate cancer and the 7<sup>th</sup> and the 11<sup>th</sup> most frequent diagnosed cancer in men and women, respectively. Overall, 75% of newly diagnosed BCa are non-muscle invasive (1), which is a disease burdened by recurrence in 60–80% of cases and progression in 10–30% of cases, depending on the tumor stage (2,3). Several risk-classification systems were developed to facilitate patients' management, and they usually include clinical and pathological characteristic which influence patients' prognosis. During the last ten years, the presence of

histological variants in BCa became increasingly important and several studies were performed especially on patients treated with radical cystectomy (RC), to assess its role in muscle-invasive BCa: all of them found histological variants related to worse survival outcomes (4). The role of histological variants in non-muscle invasive tumors was less studied but is equally important: understanding the role of variant histology in these types of tumors has a significance to assess individual management for avoiding undertreatment and progression. For these reasons, our review is focused on the role of variant histology in non-muscle invasive BCa.

## Evidence acquisition

A non-systematic Medline/PubMed literature search was done. The following items and combinations were searched “bladder cancer”, “bladder tumor”, “non-muscle invasive bladder cancer”, “NMIBC”, “histological variants” and “high risk urothelial cancer”. Meta-analysis, original articles and reviews in English language were selected.

## Classification of histological variants

The prognostic importance of variant histology in BCa was underlined by the World Health Organization (WHO), which included the category of “invasive urothelial carcinoma with divergent differentiation”, defined as urothelial cancer with presence of other morphologies, in the 2016 classifications (5). This classification includes “urothelial” and “nonurothelial” variants distinguished on the basis of pathological morphological evaluation.

Non-urothelial variants include, first of all, the squamous cell carcinoma which is frequent especially in middle eastern countries (about 30% of all BCa cases) because of the diffusion of *Bilharzia* infection in these areas (6). Microscopically is characterized by the presence of squamous pearls, intercellular bridges and keratohyalin granules (7). Macroscopically are usually monofocal tumors with big dimension, associated with leucoplakia and mainly located in the trigone (8,9). The glandular variant is the second most common nonurothelial histological variant (about 18% of muscle-invasive BCa) (10) and includes four subtype of tumors (enteric adenocarcinoma, mucinous adenocarcinoma, mixed adenoma, and villous adenoma) (11). Also the neuroendocrine variant is divided into four subgroups (small cell, large cell, well differentiated, and paraganglioma): of them, the small cell one, is the most frequent but is anyhow rare and represents about 1% only of all BCa cases (12).

Main urothelial variants include sarcomatoid, which has a prevalence of 0.3–0.6% (13,14), of all bladder tumors. At macroscopic evaluation usually occurs with a polypoid shape with haemorrhagic or necrotic areas (15). The micropapillary variant is included in this classification and has a prevalence of about 0.6–2.0% of all BCa (16): microscopically is characterized by small nests and aggregates of tumor cells within lacunae without vascular cores. The plasmacitoid variant is rare and very aggressive and in majority of cases occurs at presentation as extravescical disease with distant metastasis (17). Similarly

to plasmacitoid variant, the nested is usually associated with poor survival outcomes (18). It is characterized by irregular and confluent small nests and abortive tubules composed of urothelial cells infiltrating the lamina propria or the muscularis, usually without surface involvement (19,20).

## Accuracy of TURBT

The diagnosis of histological variants at transurethral resection of bladder (TUR), present several difficulties, probably related to the small amount of tissue obtained with the endoscopic resection and to the presence of artifacts caused by cut and the coagulation. The accuracy of TUR in the evaluation of presence and type of variant histology has been analyzed just in a few studies, which reported discordant results. Moschini *et al.* (21) using Cohen kappa coefficient to evaluate agreement between findings at TUR and RC, found a poor agreement between the two specimens. In particular the concordance depended on the type of variant histology and was low in general and micropapillary variant, and high for sarcomatoid, small cell, and squamous variants. Similar result was shown in a multicenter study by Cai *et al.* (22) who reported a lack of agreement for uncommon variants between TUR and RC in the entire population ( $P < 0.001$ ). However, Abufaraj *et al.* (23), reported a high concordance rate between the two specimens (about 84%), with a TUR’s specificity of 99% and negative predictive value (NPV) of 83%. Abd el-Latif *et al.* (24) found a sensitivity of 39% for predicting variant morphology at TUR specimen, but this rate was variable according different subtype of histological variants. The discordance between the results reported in literature is probably due to the differences in collection and analyses of pathological samples. These results underline the importance of the methodology of resection which, when possible, should include “en bloc resection” and muscularis in the sample (13).

## Treatment of non-muscle invasive histological variants

### Intravesical therapy

In general, BCa with variant histology is considered as an aggressive disease and early RC should be proposed in majority of cases of non-muscle invasive BCa. However, Bacillus of Calmette-Guerin (BCG) can be safely performed in very selected cases. The nested variant in majority of cases

appears as a muscle-invasive disease (70% of cases) (25). Linder *et al.* (25), after matching for T stage, reported no difference in survival outcomes between nested variant and pure urothelial carcinoma. Similar result were found for patients with glandular differentiation and after adjusting for stage and percentage of the variant were found to have similar survival outcomes compared to patients with pure urothelial carcinoma (26). Glandular variant has been evaluated in a study by Miller and Epstein (27) who demonstrated that six patients with glandular variant were successfully treated with BCG (27).

### Early cystectomy

Early cystectomy should be recommended in several cases of non-muscle invasive BCa with variant histology (28). This treatment should be proposed first of all, in squamous cell carcinoma even if T1 diseases are rare (19). The squamous carcinoma, therefore, was reported as significantly associated with recurrence and cancer specific mortality in patients with T1 BCa not treated with early RC (29,30). Patients with sarcomatoid variant have poor oncological outcomes with worse survival and higher cancer specific mortality compared to patients with pure urothelial carcinoma. Moreover, it usually occurs as extravesical disease at RC with high rates of local progression and distant metastasis (14,31-33). No study regarding effectiveness of intravesical treatment in this variant has been published, but according the results of before mentioned study an early RC should be proposed to these patients. Same suggestion is reserved for micropapillary carcinoma: therefore Kamat *et al.* (34) reported high rates of BCG-failure (67%) with 22% of patients who developed distant metastasis and no patients treated with delayed RC was alive at 10 years (35). When analyses was focused on non-muscle invasive BCa they reported worse survival outcomes for patients treated with BCG compared to those treated immediate RC (36). Similar results were reported by Ghoneim *et al.* (37) who analyzed data of ten patients with micropapillary BCa. Seven patients were treated with BCG, all had a recurrence and 6 of them had a pT3 disease at RC with node involvement (37). A recent meta-analysis analyzed patients with T1 micropapillary BCa and reported a 5-year cancer specific survival rate between 60% and 85% in patients treated with resection plus BCG instillation and from 81% to 100% in patients treated with early RC (38). Since plasmacitoid variant is very aggressive and chemosensitive (39) an early RC plus neoadjuvant/adjuvant therapy should be

proposed (40). Same suggestion for the small cell carcinoma in which RC should be proposed also for non-muscle invasive disease.

### Conclusions

The diagnosis of histological variants at TUR specimen is difficult, probably due to the small account of tissue obtained through endoscopic resection and presence of artifacts related to coagulation and cut. The presence of variant histology is usually associated with advanced diseases and poor oncological outcomes. In the majority of case of variant histology and in particular in case of sarcomatoid, plasmacitoid, micropapillary and neuroendocrine non-muscle invasive tumors, immediate RC should be suggested. In case of glandular or nested differentiation BCG treatment can be safely proposed.

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### Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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