Original Paper

# Assessment of Histopathological Parameters Useful in the Diagnosis of Low Grade Non-Invasive Urothelial Carcinomas

ANDREI ȘTEFAN SĂNDULESCU[1], ALEX EMILIAN STEPAN[2], CLAUDIU MĂRGĂRITESCU[2], ANDA ELENA CRIȘAN[3], CRISTIANA EUGENIA SIMIONESCU[2]

[1]PhD Student, Department of Pathology, University of Medicine and Pharmacy of Craiova, Romania

[2]Department of Pathology, University of Medicine and Pharmacy of Craiova, Romania

[3]Department of Oncology, University of Medicine and Pharmacy of Craiova, Romania

**ABSTRACT:** Urothelial papillary lesions of urinary bladder are frequent lesions in medical practice and sometimes difficult to be histopathologically classified. In this study were included 179 urothelial papillary lesions, represented by low grade non-invasive urothelial carcinomas (LGNIUC), papillary urothelial neoplasms of low malignant potential (PUNLMP) and urothelial papillomas (UP), for which the architectural and cytological histopathological parameters were analyzed in order to determine their usefulness for the classification of lesions. For each parameter, an aggressivity score was set, the sum representing the composite histological score (CHS) for each case. The increase of urothelial thickness, the papillae fusion, the loss of cellular polarity, loss of basal cell palisading and absence of umbelliform cells were commonly associated with diffuse pattern in LGNIUC, were focal/absent in PUNLMP and absent in UP. The nuclear hypertrophy and hyperchromasia, the nucleoli presence and mitotic activity were specific for LGNIUC, rarely associated with PUNLMP and absent/low in UP. CHS values for the three categories of analyzed lesions were superior statistically significant in LGNIUC compared to PUNLMP and UP. The mitotic index and the thickness of cytological atypical epithelial layers support the parameters utility as reproducible criteria for the differentiation of papillary urothelial tumors.

***KEYWORDS:*** *Low grade non-invasive urothelial carcinomas, histopathology*

## Introduction

About 75% of bladder cancers are non-muscle-invasive, the majority being represented by urothelial carcinomas [1], of which 70% are non-invasive low-grade tumors.

Non-invasive urothelial papillary neoplasms with bland cytology are various and often difficult to be grouped, their classification system being over time a problem subjected to many debates.

Several classification systems have been proposed for their grouping in an attempt to more accurately predict recurrence and tumor progression.

The 2004 WHO/ISUP (World Health Organization/International Society of Urological Pathology) classification system describes in detail the architectural and cytological characteristics specific to each non-invasive papillary urothelial neoplasia category [2].

WHO 2016 continues to recommend this classification, but non-invasive urothelial lesions are better defined [3], and as a result, it is expected that in the course of time, higher interobserver reproducibility will be obtained.

The management of patients with non-invasive urothelial papillary tumors is largely dependent on histopathological degree of tumors. The intraobservatory variability is quite large, even among experienced pathologies, despite efforts to develop a pathological classification that better reflects the clinical behavior [4-12].

Patients with these neoplasias have a high recurrence risk (31-78%) after transurethral resection, and a subgroup of them has increased tumor grade and/or stage and requires cystoscopy to detect recurrences [13-17].

If urothelial papilloma (UP) is considered a benign lesion with low recurrence risk and without progression risk, the papillary urothelial neoplasm of low malignant potential (PUNLMP) involves a quite high risk for recurrence (<50%), but with low risk for progression (<5%), while non-invasive low grade urothelial carcinomas (LGNIUC) involve a high recurrence risk of approximately 50% and a low progression risk of 5-10% [12].

We proposed the evaluation of some histopathological parameters useful in LGNIUC diagnosis, and similarly related lesions, represented by PUNLMP and UP.

## Material and Methods

The present study included 179 non-invasive urothelial papillary lesions, the biological material being represented by tissue samples obtained by transurethral resection during cystoscopy, from patients with bladder tumor suspicion admitted to the Urology Clinic of Emergency County Clinical Hospital Craiova.

The tumor fragments were fixed in 10% buffered formalin, processed by the usual technique of paraffin embedding and hematoxylin-eosin staining in the Pathology Laboratory of the same hospital.

We followed the quantification of histological parameters used by the WHO workgroup for the classification of urothelial papillary lesions [3], as well as some parameters that can be used for the differential diagnosis of these lesions through our experience.

For each analyzed parameter, a grading system between 0-2 was used as follow: number of cellular layers on papillae (papillae thickness) (0<7, 1>7 focally, 2>7 diffuse), papillae fusion (0-absent, 1-focally present, 2-diffuse present), cellular polarity (0-present, 1-focally loss, 2-diffuse loss), basal cell palisading (0-present, 1-focally loss, 2-diffuse loss), umbelliform cells (0-present, 1-focally loss, 2-absent), nucleoli presence (0-unidentifiable, 1-poorly visible, 2-clear visible), nuclear hypertrophy and hyperchromasia (0-absent, 1-focally present, 2-diffuse present), mitosis rate/10HPF (high power field)/x400 (0-≤1, 1-≤2, 2->2).

The assessment was done by two experienced pathologists (CES, AES), the final score being set only after the re-evaluation of inconsistent cases.

Subsequently, we calculate the composite histological score (CHS), which represented the sum of the scores assigned to each parameter.

The statistical analysis used mean values and comparative chi square test ($\chi 2$) in the SPSS 10 automatic software.

The study was approved by the local ethical committee (No.79/16.04.2019), and written consent was obtained from all patients.

## Results

The histopathological analysis of the 179 cases included in this study indicated the presence of 120 cases (67%) of low grade non-invasive urothelial carcinomas (LGNIUC), 41 cases (22.9%) of papillary urothelial neoplasm of low malignant potential (PUNLMP) and 18 cases (10.1%) of urothelial papilloma (UP).

The analysis of histopathological parameters regarding the architectural and cytological atypia is shown in Table 1.

***Table 1. Mean values of histological variables and CHS.***

| Variables | Grading | UP | PUNLMP | LGNIUC |
|---|---|---|---|---|
| Papillae thickness | 0 | 18 | 0 | 0 |
| | 1 | 0 | 36 | 0 |
| | 2 | 0 | 5 | 120 |
| Papillae fusion | 0 | 18 | 30 | 0 |
| | 1 | 0 | 11 | 32 |
| | 2 | 0 | 0 | 88 |
| Cellular polarity | 0 | 18 | 41 | 0 |
| | 1 | 0 | 0 | 29 |
| | 2 | 0 | 0 | 91 |
| Basal cell palisading | 0 | 18 | 12 | 0 |
| | 1 | 0 | 29 | 0 |
| | 2 | 0 | 0 | 120 |
| Umbelliform cells | 0 | 18 | 34 | 0 |
| | 1 | 0 | 7 | 0 |
| | 2 | 0 | 0 | 120 |
| Nucleoli | 0 | 18 | 41 | 81 |
| | 1 | 0 | 0 | 37 |
| | 2 | 0 | 0 | 2 |
| Nuclear hypertrophy and hyperchromasia | 0 | 18 | 5 | 0 |
| | 1 | 0 | 36 | 37 |
| | 2 | 0 | 0 | 83 |
| Mitosis rate | 0 | 18 | 0 | 0 |
| | 1 | 0 | 41 | 0 |
| | 2 | 0 | 0 | 120 |
| CHS values | - | 0 | 2-7 | 10-16 |

In the study, the 120 cases diagnosed with LGNIUC indicated a constant and diffuse increase in the papillae number of cell layers (mean score 2), constant papillae fusion (mean score 1.73), focally or diffuse polarity loss (mean score 1.75) and basal cell palisading loss (mean score 2). Umbelliform cells were absent (mean score 2).

Cytological atypia analysis has focally revealed the nucleoli presence (mean score 0.34), the presence of nuclear hypertrophy and hyperchromasia with focally or diffuse pattern (mean score 1.60), along with frequent typical mitoses disposed randomly in the urothelial thickness but also rare atypical mitosis (mean score 2, mean number of mitosis 4.41) (Figure 1).

CHS for these cases had the highest values, ranging from 10-16, with an average value of 13.44.


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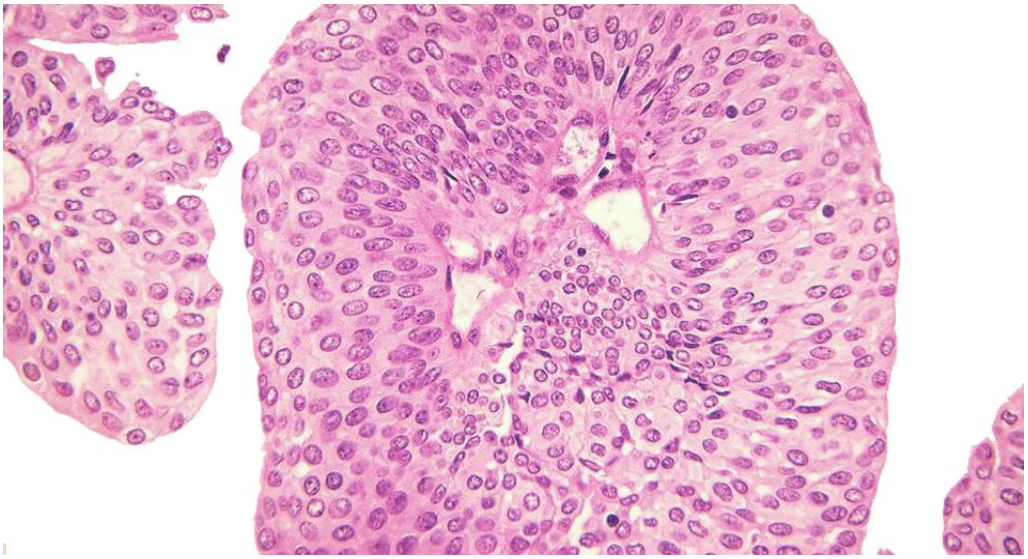

***Figure 1. LGNIUC, HE staining, x40.***

In contrast, the 41 cases of PUNLMP were characterized by elongated papillae, lined by urothelium with increased cellular stratification (mean score 1.12), rarely fused (mean score 0.26) and with polarity preserved in all cases. The basal cell palisading (mean score 0.70) as well as the presence of umbelliform cells (mean score 0.17) was frequently identified. Cellular atypia represented by nuclear hypertrophy and hyperchromasia was reduced, focally and only rarely identified (mean score 0.87), unidentifiable nucleoli and reduced mitotic activity (mean score 1, mean number of mitosis 1.51), mitosis being limited to the basal layers (Figure 2). CHS for PUNLMP varied between 2-7, with an average value of 4.14.

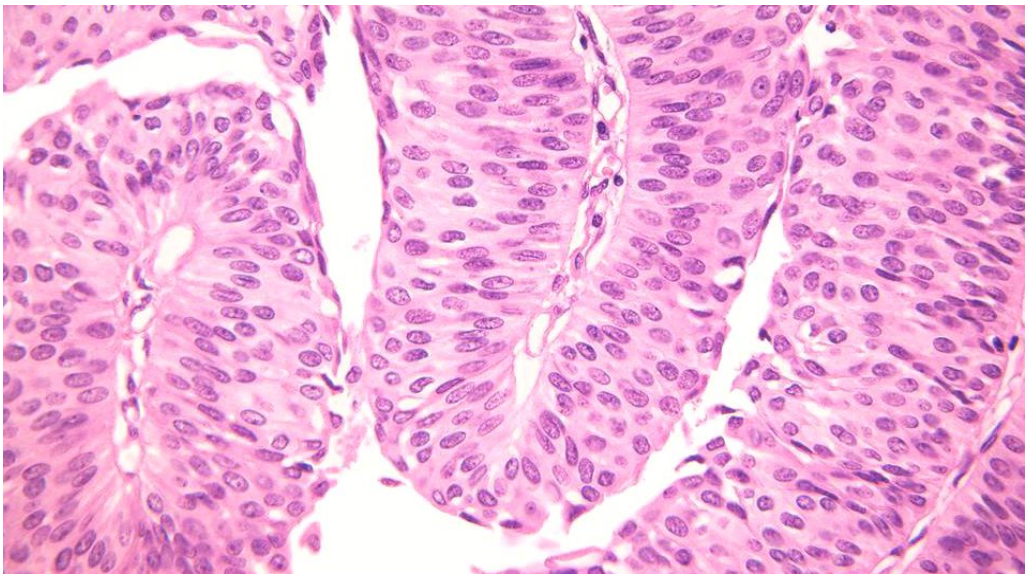

***Figure 2. PUNLMP, HE staining, x400.***

Finally, the analysis of the 18 UP cases has consistently revealed clear benign lesion characteristics. The papillae were covered by urothelium similar to normal, without papillary fusions, with preserved polarity, and the basal palisading as well as the presence of umbelliform cells were consistently present. Cellular atypia was absent and the mitotic activity was below 1 mitosis/10 HPF, limited to the basal layers (mean score 0, mean number of mitosis 0.17) (Figure 3). CHS for UP was 0 in all cases.

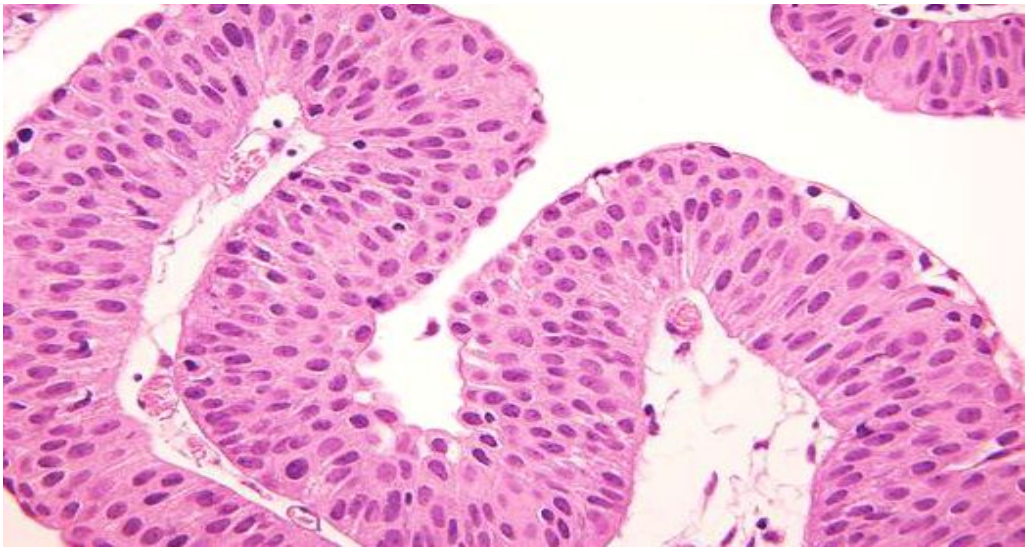

***Figure 3. UP, HE staining, x400.***

Statistical analysis of CHS values for the three analyzed lesions, indicated significantly higher values for LGNIUC compared to PUNLMP and UP ($p<0.001$, $\chi 2$ test) (Figure 4).

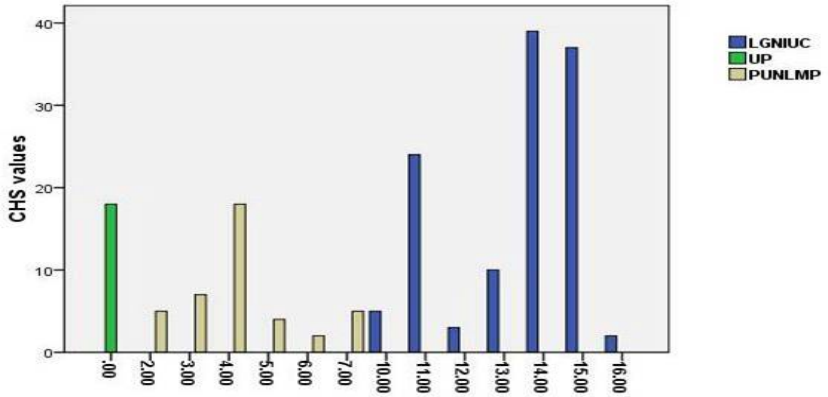


***Figure 4. CHS values distribution depending on lesion type.***

## Discussions

Classification of urothelial tumors is of particular importance in non-invasive urothelial disease, especially for papillary neoplasms. In the third edition, the WHO officially adopted for non-invasive papillary lesions the 1998 ISUP system, with the four categories: papilloma, PUNLMP, low grade urothelial papillary carcinoma, and high grade papillary urothelial carcinoma, for the latter with the possibility to specify diffuse anaplasia when present [2].

This classification system, called the WHO (2004)/ISUP system, was widely accepted by the Armed Forces Institute of Pathology on the Urinary Bladder [18], the 7th edition of the AJCC Cancer Staging Manual [19], the Association of Directors of Anatomic and Surgical Pathology, the College of American Pathologists [10], and European Protocols [20] because it eliminates the ambiguity of older classification systems [12,21].

The WHO (2004)/ISUP system, and the later 2016 system, describes in detail the characteristics of each category of non-invasive papillary urothelial neoplasm [2,3].

However, from a pathological point of view, the diagnostic limit between stage 0 (Ta) low grade papillary urothelial carcinoma and the non-carcinoma group is rather vague [21].

In this study we analyzed the architectural atypia by evaluating the urothelium thickness, the papillae fusion, the loss of polarity, the basal cells palisading and the presence of umbelliform cells. In UP all cases had normal stratification, in PUNLMP they have constantly increased focal or diffuse, while in LGNIUC an increased constant and diffuse number of layers was observed. The papillae fusion and loss of


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polarity were absent in UP, rarely focally present in PUNLMP, and constant focal or diffuse present in LGNIUC. The basal cell palisading has been identified in all cases of UP, only rarely absent and focal in PUNLMP and constantly absent in LGUCNI. Umbilical cell layer analysis revealed their presence in UP, rarely absent and only focal in PUNLMP, and the absence of this focal layer or more frequently diffuse in LGNIUC.

However, some features can be subjectively assessed in routine histological staining. In practice, when only a small amount of biopsy material is available for examination or when transurethral resections are examined, there may be a large overlap of the histopathological characteristics between UP, PUNLMP and LGNIUC. Several studies on papillary urothelial tumors have reported a severe discrepancy for the PUNLMP diagnosis even for the most experienced uropathologists [22,23].

Cytological atypia is thought to be more reproducible than architectural atypia [24].

Architectural atypia, such as the thickness of more than seven layers and the papillae fusion, are very useful in distinguishing UP from PUNLMP, but sometimes their assessment can be confused due to tangential sections [25].

Thus, urothelium thickness estimation may become subjective in the case of tangential papillae section, which is why the assessment should be performed only on longitudinal sectioned papillae and in the absence of electrical artefacts [12].

In addition, thin fibrovascular axes are considered a distinctive sign of urothelial neoplasia [26], and their presence, even in rudimentary form, in biopsies under surveillance, must be indicative for neoplastic persistence or recurrence [12].

The basal cells palisading in each papillary structure may be useful in the PUNLMP diagnosis, while cell epithelioid characteristics versus fusiform ones may be arguments in favor of LGNIUC versus PUNLMP or UP [24].

However, it is considered that the loss of umbelliform cells, the conservation of nuclear incisions, are too subjective and less reproducible characteristics and should be excluded from the algorithm for the incidence of these tumors [24].

Also, the presence of continuous or focal, or absence of the umbelliform cell layer, can argue the diagnosis of PUNLMP or UP. However, it must be taken into account that the absence of umbilical cells may be caused by either surgical manipulation or during orientation of the tissue specimen [12].

Analysis of cytological atypia for urothelial papillary lesions included evaluation of nuclear hypertrophy and hyperchromasia, the presence or absence of nucleoli, and mitotic activity. The nuclear hypertrophy and hyperchromasia was absent in the case of UP, only rarely and focal in PUNLMP and constantly focal or diffuse in LGNIUC. The analysis of nucleoli presence of allowed their focal or rarely diffuse observation only in LGNIUC. The assessment of mitosis number indicated an average of 0.17 for UP, 1.51 for PUNLMP and 4.41 for LGNIUC. UP has rarely presented mitosis, always typical, located near the basal layer of the urothelium. In case of PUNLMP, we observed more frequently the presence of typical mitosis, located near the basal layer of the urothelium. In contrast, in LGNIUC we noticed frequent typical mitosis randomly arranged in the urothelium thickness, but also rare atypical mitosis.

Mitotic activity represents a reliable marker for classification of urothelial lesions [27] and may play an adjuvant role in the prediction of recurrence or invasiveness [21].

Zhang XK et al. demonstrated in a multivariate analysis that the presence of mitosis is a significantly independent biomarker for non-recurrent survival and progression free survival [28]. The authors reported that mitosis, although rare in PUNLMP, their presence is an unfavorable independent prognostic indicator [28].

Several studies have shown that P53 and MIB-1 had prognostic significance for patients with PUNLMP and LGNIUC [29,30], and mitotic activity greater than≥5/1HPF is a strong predictor of recurrence in pTa papillary urothelial carcinomas [31].

However, some studies appreciate that immunostaining did not provide significant advantages compared to the assessment of mitoses by the usual microscopy [28].

Therefore, the mitotic activity could be considered as a marker for prognosis assessing of lesions [24,28].

The heterogeneity of lesions with variable morphology between PUNLMP and LGNIUC, and the grouping difference are less clinically important given the relatively similar rates of recurrence. In contrast, the implications of association of low-and high-grade noninvasive carcinomas are more clinically important, both mixed models PUNLMP/LGNIUC/HGUNIC being common [32].

In reviewing of the "complicated" cases, it is important that the assessment to be done on thin, well-stained sections, the judicious ordering of the serial sections being useful in such cases [12].

An error source for the classification of non-invasive papillary lesions could be the variability of histological characteristics evaluated in a TUR specimen. In general, the classification based on the dominant model rather than the one based on the higher tumoral grade could lead to the under-grading of the lesions [33].

Therefore, it remains to be investigated whether a small area (e.g.<5%) of a higher-grade model affects the prognosis of patients. Some experts have expressed the concern about the increased trend of pathologists for assessing non-invasive lesions as high-grade lesions [12].

Finally, it is strongly recommended the intercollegiate consultation of difficult or limiting cases, especially since there are no immunohistochemical markers or reliable molecular markers that can be recommended as validated adjuvants for the diagnosis [12].

Perhaps future advances in the molecular classification of these tumors will change the traditional morphological classification, allowing for a more accurate and objective assessment of the biological potential of these tumors, the accurate histopathological assessment being an essential step in the management of non-invasive urothelial neoplasms.

## Conclusions

The mitotic index and the thickness of the cytological atypical layers prove to be useful as the reproducible parameters of the scoring algorithm to differentiate between papillary urothelial tumors.

Based on the scoring algorithm, PUNLMP can be histologically classified as an intermediate step between UP and LGNIUC.

### Conflict of interests

None to declare.

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***Corresponding Author: Alex Emilian Stepan, Department of Pathology, University of Medicine and Pharmacy of Craiova, 66 1 May Avenue, 200628 Craiova, Romania, e-mail: astepan76@yahoo.com***