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Review

Invasiveness or growth pattern in urothelial tumours. A perspective to rethink the current WHO classification

Jiyeon Lee[1], Sangjoon Choi[2], Ghee Young Kwon[3]

[1] Department of Diagnostic Pathology, Samkwang Medical Laboratories, Seoul, Republic of Korea; [2] Pathology Center, Shinwon Medical Foundation, Gwangmyeong-si, Republic of Korea; [3] Department of Pathology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea

Summary

According to the current WHO classification, urothelial tumors consist of non-invasive urothelial neoplasms and invasive urothelial carcinoma which is supposed to include all tumors with invasion regardless of extent and pattern. Some pathologists are uncomfortable about such all-inclusive definition of invasive urothelial carcinoma and it is questionable whether invasiveness is a valid defining feature for primary distinction of urothelial tumors. Considering that most pathologists understand urothelial tumors based on the dual-track pathway model, we would like to raise concern that it may be necessary to rethink the validity of the current WHO classification compared to the restructuring into papillary vs non-papillary tumors. In our opinion, such restructuring would align the WHO classification with the pathogenesis model and could clarify the diagnostic terminology regarding invasiveness. The term of urothelial carcinoma in situ may also be reconsidered.

Key words: WHO classification, papillary, invasive, urothelial carcinoma, urothelial carcinoma in situ

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Correspondence
Ghee Young Kwon
E-mail: geeo@skku.edu

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Introduction

For pathologists, the World Health Organization (WHO) classification of tumors provides a solid basis for general understanding of the tumours and dictates the essential elements of everyday diagnosis. However, in urothelial carcinoma (UC), there is a major discrepancy between the current WHO classification and the widely acknowledged pathogenesis model since the primary distinction of the former is between invasive vs non-invasive urothelial neoplasms[1] and the latter understands UC as developing in papillary and non-papillary pathways[2] (Figs. 1, 2). If they were to align with each other, the WHO classification should be restructured into papillary vs non-papillary tumors and therefore, in this opinion paper, we would like to appraise the pros and cons of the possible restructuring of the WHO classification compared to the maintenance of status quo. We do not intend to argue that the current classification should be modified, but would like to suggest that it may be necessary to evaluate the validity of the incorporation of the widely-acknowledged dual-track

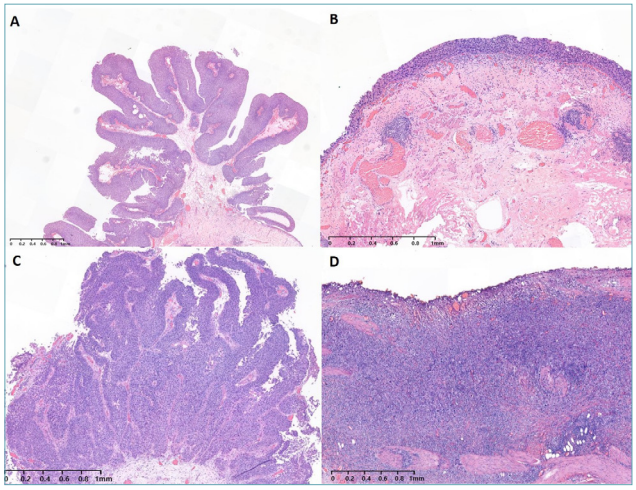

Figure 1. Low-power images of typical (A) papillary, non-invasive (B) non-papillary, non-invasive (C) papillary, invasive (D) non-papillary, invasive urothelial tumors.

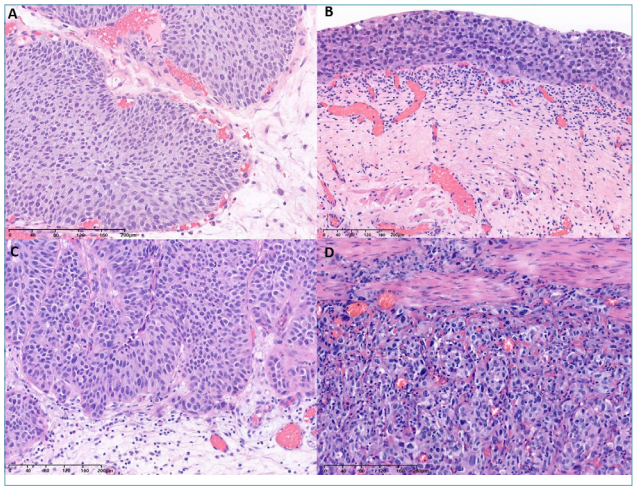

Figure 2. High-power images of the same cases as in Figure 1. (A) papillary, non-invasive (B) non-papillary, non-invasive (C) papillary, invasive (D) non-papillary, invasive urothelial tumours.

pathogenesis concept into the WHO classification of urothelial tumors.

Invasive or non-invasive

One of the issues with the current WHO classification would be the definition of invasive urothelial carcinoma which constitutes the larger group for the primary distinction (Tab. I). Invasiveness of the tumor is one of the most important prognostic features as demonstrated in its incorporation into the pathologic tumor stage in almost all entities of carcinoma and invasion of carcinoma from surface-lining epithelium is observed in continuous spectrum ranging from minimal outpouching out of basement membrane to overt infiltration into surrounding tissue. Such a wide range of invasion is sometimes sub-classified with the introduction of micro-invasion as in carcinomas of breast or uterine cervix. Although micro-invasion has not been officially defined in UC, it would not be an unfamiliar concept in this tumor considering that the extent of invasion has been shown to be a significant prognostic factor in urothelial carcinoma which invades sub-epithelial connective tissue and that there is ongoing discussion regarding how to sub-stage the early tumor invasion before infiltration into the proper muscle layer[3].

Invasive carcinoma literally means carcinoma with invasion regardless of the extent of the invasion, although, it generally carries a connotation of significant invasion. This connotation is indirectly supported by the concept of micro-invasion since “plain” invasion is supposed to apply to something more advanced than micro-invasion. Also considering that urologists and researchers once used invasive UC as contrasted to superficial tumors which include superficial invasive tumours[4,5], it may be confusing, at least to pathologists who have been practicing for over a decade or familiar with pathology of breast or uterine tumors, to use invasive UC in its literal meaning as in the current WHO classification. Consequently, some pathologists are reluctant with the diagnosis of invasive UC for tumors with minute invasion and resort to alternative forms of diagnosis which do not conform to the WHO-defined categories. Still others prefer to append

Table I. Comparison of the current WHO classification of urothelial tumors with the morphologic features according to the dual-track pathway model. (Invasive tumors of different features are included in the invasive UC in the current WHO classification.)

WHO classification	Real world presentation as in dual-track model
Non-invasive urothelial neoplasms	Papillary lesions
- Urothelial carcinoma in situ	- Non-invasive
- Low-grade PUC	- Microinvasive
- High-grade PUC	- Invasive
- PUNLMP	Non-papillary lesions
Invasive urothelial neoplasms	- Non-invasive
	- Microinvasive
	- Invasive

PUC; papillary urothelial carcinoma, PUNLMP; papillary urothelial neoplasms of low malignant potential.

additional information regarding the extent of invasiveness after the main diagnosis and these varying approaches result in some inconsistency in the application of diagnostic terminology among pathologists which will be elaborated later. It would not be ideal to employ a criterion for primary classification of tumours if the criterion is not received with the same interpretation as is the case with the invasive UC.

Another problematic aspect with the current classification is illustrated by the biopsy diagnosis of papillary tumors which show invasion in some specimens but not in others. It is awkward to diagnose a case as non-invasive urothelial neoplasm in one specimen and invasive UC in others when the overall appearance is not much different between the specimens. While the main diagnosis is supposed to address essential characteristics of tumors, invasiveness is one presenting feature of tumors which is not uniform across one tumor and thus often varies between multiple specimens from one case. Therefore, it cannot be readily considered as an essential feature of the tumor which can serve as a criterion for primary distinction of urothelial tumors and it may be worthwhile to consider the modification of the current WHO classification of urothelial tumors which is primarily divided into two groups of invasive vs non-invasive urothelial neoplasms.

Papillary vs non-papillary

The most important issue would be the relative importance of the growth pattern of a tumor compared to the presence of invasion. Currently, the pathogenesis of UC is comprehended in the dual-track pathway model of papillary and non-papillary lesions/tumors although a third pathway also appears to make some contribution. This model based on the growth pattern reasonably reflects the diverse morphologic features of the tumor encountered by pathologists in routine daily practice and constitutes the main backbone of our understanding of UC starting as early as from the pathology textbooks for medical students[6] and is supported by molecular characteristics as well as morphological features[2]. Therefore, the growth pattern of the tumor would be a perfect candidate for the main classifier of UC and its validity could be measured against that of the present criteria which is the presence of invasion.

If we use the growth pattern as the primary classifier and restructure the classification, the reshuffled WHO classification would consist of two groups of tumors showing different growth pattern, each with varying extent of invasion (Tab. II). Compared to the current classification, it would be a more balanced structure composed of two equivalent large entities of distinct morphologic and molecular features with matching subdivisions according to the extent of invasion. Therefore, if we make a diagnosis according to this restructured classification, the growth pattern and the presence/extent of invasion could be neatly incorporated into the diagnosis and it would be a stable framework which can be translated readily into daily practice.

Table II. Possible restructuring of WHO classification of urothelial tumors to align with the dual-track pathway model. (Entities in parenthesis need to be discussed regarding their inclusion and nomenclature.)

Papillary urothelial lesions
- (Papillary urothelial hyperplasia)
- Urothelial papilloma
- Papillary urothelial neoplasm of low malignant potential
- Low-grade papillary urothelial carcinoma
- High-grade papillary urothelial carcinoma
- (Papillary invasive urothelial carcinoma)
Non-papillary urothelial lesions
- (Urothelial dysplasia)
- Urothelial carcinoma in situ
- Invasive urothelial carcinoma

On the other hand, with the current classification, the primary distinction yields a disproportionate grouping as regards pathologic spectrum since non-invasive lesions/tumors are confined in a narrow bin while invasive carcinoma includes tumors with all manners of invasion. In addition to being disproportionate, the grouping is also confounded since some portion of one group is more similar to tumors in the other group in essential characteristics, as seen in papillary UC with minute invasion which will be discussed separately in the next section. Moreover, since invasive UC covers a wide spectrum of tumors, it needs further specification and it is evident that the specification should include the extent of invasion. The main diagnosis of tumors is supposed to carry the essential piece(s) of information regarding the characteristics of the tumor and it is inefficient use of valuable space to occupy it with information which needs further elaboration as in invasive UC with invasion into sub-epithelial connective tissue. Thus, some pathologists opt to make the diagnosis out of WHO-defined categories as revealed in our survey among Korean pathologists most of whom were general pathologists (data not published) and the results of the survey will be described in the next section.

Primary classification of a tumor usually addresses essential defining characteristics of the tumor such as HPV-association in squamous cell carcinomas of

the male and female genital organs which can form distinct pathologic groups[7,8]. On the other hand, although invasiveness of a tumor is one of the most powerful morphologic prognosticators, it is present in continuous spectrum in UC and does not form distinct groups unlike ductal carcinoma of breast which is classified into ductal carcinoma in situ and invasive ductal carcinoma. Therefore, in our opinion, its value in pathologic aspects as a primary classifier for UC is questionable. The basic concept of the current WHO classification of urothelial tumors was introduced in the 2nd WHO bluebook published in 2004 when the dual-track pathway model was not yet universally accepted. Thus, it appears that there should have been discussion whether to align the WHO classification with the pathogenesis model.

Papillary UC with minute invasion

Every pathologist is familiar with this scenario although the incidence of such tumors is hard to pin down due to the absence of unified terminology and solid criteria. In our opinion, this group of tumors represent the problematic areas of the current classification in multiple aspects. Firstly, in a pathologic perspective, the tumors confound the classification since they resemble non-invasive papillary UC more than the invasive UC while they belong to the invasive UC in the current classification. This resemblance is dramatically highlighted by the considerable inter-observer variability in the diagnosis of stromal invasion in papillary UC which means that they can resemble each other in such extent that it is sometimes difficult to decide whether the tumor is non-invasive papillary UC or invasive UC (Fig. 3).

For clinicians likewise, this group of tumor is handled together with non-invasive papillary UC as one component of non-muscle invasive bladder cancer (NMIBC) and is managed separately from the other types of invasive UC in muscle-invasive bladder cancer (MIBC) group of tumors. Therefore, it is not surprising that a considerable proportion of pathologists are not comfortable about calling such tumors as invasive UC. In our survey for the diagnostic terminology for papillary UC with minute invasion, 49.1% (28 of 57) of pathologists rendered a diagnosis of invasive/infiltrating UC and papillary UC with (micro)-invasion was used in 43.9% (25 of 57). The remaining 7.0 % (4 of 57) diagnosed such tumors as invasive/infiltrating papillary UC. This variation in the application of diagnostic terminology means that a considerable proportion of pathologists think that the current WHO classification has some unresolved issues in the diagnosis of such cases.

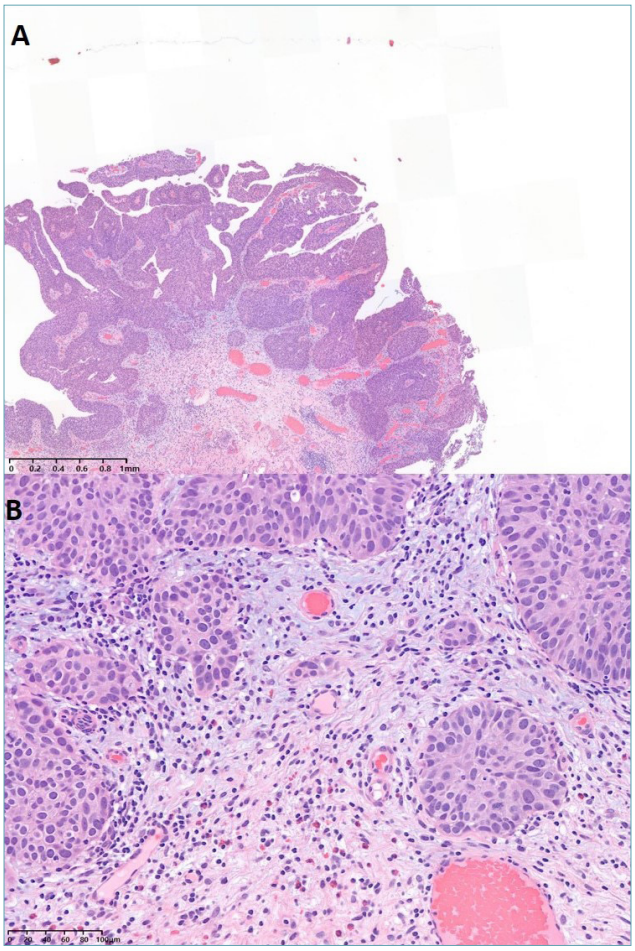

Figure 3. Low- and high-power images of a papillary tumor with minute invasion. On low power the histologic appearance is similar, or almost identical, to papillary non-invasive UC (A). Invasive tumor cells and nests are found in the stroma (B). There is likely to be differing opinions regarding the presence/extent of the invasion in this picture, which can be regarded as implying that the presence of invasion may not be the best classifier for the primary distinction of urothelial tumors.

Current WHO vs incorporation of dual-track concept

One rationale for the current classification into non-invasive lesions and invasive carcinomas appears that there are several common elements shared between tumors of both papillary and non-papillary pathways such as variant histology and dysplasia and so on which may be better addressed as a group encompassing both pathways. However, it would not be a serious challenge to cope with such elements even if we modify the system deletion and in our opinion, there is insufficient advan-

tage in the current WHO classification compared to the possible restructuring based on the growth pattern.
One problem to be expected in the modification based on the growth pattern will be that there are cases with mixed or indistinct growth pattern, especially in deeply invasive tumors. In such cases, the distinction could be either non-committal or based on some loose criteria. Hence, we doubt that this would be a shortcoming and our argument is more for the inappropriateness of invasiveness as a defining criterion for primary distinction than for the adoption of growth pattern. In this context, we think that simple elimination of non-invasive vs invasive scheme may also be considered as an alternative.
If the WHO classification is restructured based on the new perspective, there would be some entities to sort out regarding their definition or nomenclature. Papillary urothelial hyperplasia may be one example since it can be included as papillary pre-neoplastic lesion. Further discussion may be reserved for later when the restructuring/modification is decided, although we would like to offer our opinion regarding one other important entity, which is urothelial carcinoma in situ.

Urothelial carcinoma in situ

If the WHO is restructured, it might also be necessary to reconsider the term for non-invasive, non-papillary carcinoma which currently is UC in situ, which has limited extensibility for tumors with invasion because of the “in situ” part of the term. Since invasion beyond basement membrane is inevitably present in some cases, the terminology should be available for such cases and if we call those tumors as UC in situ with invasion or (micro) invasive UC in situ, it may appear self-contradictory. Similar incongruity has been resolved in breast tumors with the introduction of micro-invasive ductal carcinoma instead of ductal carcinoma in situ with micro-invasion [9]. In our opinion, one cause of this problem is the fact that UC situ is an inadequate term in that it not only fails to capture the essential features of the tumor it is supposed to represent but also carries false connotation regarding them. That is, while the quintessential characteristics of urothelial carcinoma in situ would be that it is non-papillary and high grade, the term UC in situ implies neither of these. Moreover, the term is counter-intuitive to the propensity of invasion and the capacity for lateral spread which is frequently displayed by the tumor (Fig. 4). Therefore, it would be worth the effort to discuss the validity of changing it to something more in keeping with the essential features of the tumor, especially if we consider modification of the WHO classification to incorporate the dual-track concept.

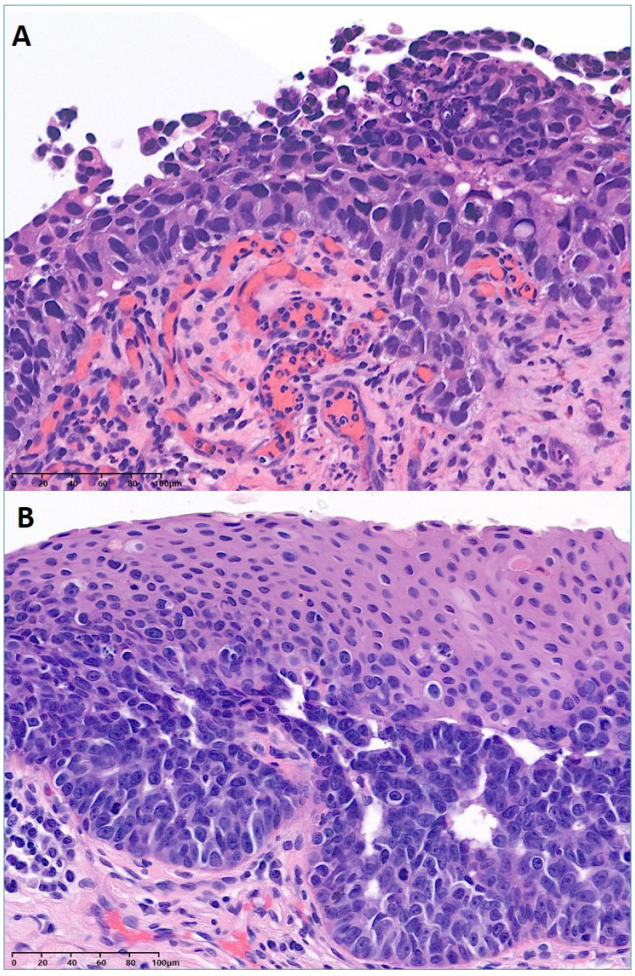

Figure 4. Two cases of urothelial carcinoma in situ showing stromal invasion (A) or lateral spread underneath the squamous epithelium of penile urethra (B), which is not readily compatible with the literal meaning of “in situ”.

Although the term UC in situ is deeply entrenched in medical terminology and well-known to clinicians, the names for similar entities have been changed in biliary tract [10], uterine cervix and vagina and penis [11]. So why not in urinary bladder and ureter? Granted that UC in situ has been in use longer than the previous names of the aforementioned entities and does not have serious contender, it will not be impossible to change the nomenclature if it is universally agreed that the term is vastly incongruous with the characteristics of the tumor it is supposed to signify. Specific nomenclature would be a matter of long discussion but one obvious candidate would be intraepithelial lesion with some appropriate qualifiers similar to other organs.

Conclusion

We propose to rethink the current WHO classification of urothelial tumors to evaluate the validity of the incorporation of the dual-track pathogenesis model. In our opinion, such restructuring would better reflect the morphologic features of the tumor and could help to clarify the diagnostic terminology regarding tumor invasiveness. Validity of the term UC in situ may also be reconsidered.

Conflicts of interest statement

The authors declare no conflict of interest.

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Authors' contributions

Conceptualization: GK. Supervision: GK, JL. Manuscript-drafting: JL, SC.
Manuscript-review and editing: all authors.
JL and SC contributed equally to this work.

Ethical consideration

As a review article, the present study is exempt from ethical approval.

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