# UROTHELIAL NEOPLASIA OF THE URINARY BLADDER – COMPARISON OF INTEROBSERVER VARIABILITY FOR WHO CLASSIFICATION 1972 WITH WHO/ISUP CONSENSUS CLASSIFICATION 1998

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**Background:** Classification of urothelial bladder tumours is an important factor in the treatment and prognosis of these lesions. Over the years many classifications have been proposed for this purpose. The objective of this study was to classify urothelial neoplasms of the urinary bladder using the latest WHO/ ISUP Consensus Classification 1998 and WHO Classification 1972 and compare the two regarding interobserver variability. **Methods**: This study included 100 consecutive biopsy specimens of urothelial neoplasms of the urinary bladder diagnosed at the department of Histopathology, Armed Forces Institute of Pathology, Rawalpindi. These were classified according to WHO Classification 1972 and WHO/ISUP Consensus Classification 1998 by 2 groups of pathologists independently. The tumour categories for WHO classification 1972; papilloma, and transitional cell carcinoma (TCC) grades I, II and III were compared with the WHO/ISUP Consensus Classification entities of papilloma, papillary neoplasm of low malignant potential, low grade and high grade papillary carcinomas. Kappa statistics were used to evaluate interobserver variability. Chi square test was used to calculate significance. **Results**: There was agreement on 80 tumours between the two groups of histopathologists when using WHO classification 1972 while there was agreement on 95 tumours using WHO/ISUP consensus classification. The value of Kappa for WHO Classification was 0.68 (good agreement) whereas for WHO/ISUP Consensus Classification it was 0.91 (excellent agreement). The difference between the two systems was statistically significant ($p<0.001$). Kappa values were less for benign and borderline lesions using both systems. **Conclusions:** WHO/ISUP Consensus Classification 1998 showed less interobserver variability than WHO Classification 1972 in the evaluation of bladder tumours . It was found easier to apply by both groups. There was less agreement on the benign and borderline lesions using both the classifications.

**Key Words**: Transitional cell carcinoma, Urinary bladder neoplasms, Urothelial neoplasia.

## INTRODUCTION

Urinary bladder cancer is the fourth most common malignancy following prostate, lung and colorectal cancer.[1] It is a major challenge in clinical oncology due to its high frequency. Although the incidence varies in different countries, bladder cancer constitutes a worldwide public health problem.[2,3] Despite all the modern modalities of diagnosis and treatment available in the new millennium, it still continues to exact a high toll in morbidity and mortality.[4]

Classification of these tumours is an important prognostic factor.[5] The first ever-grading system to classify urothelial tumours was proposed by Broders in 1922.[6] It was based on the percentage of tumour cells that were differentiated i.e; they resembled normal urothelial cells.

The first widely used grading system was proposed by Ash[7] in 1940. He divided bladdder tumours into four grades (grade I- grade IV). A popular WHO Classification was introduced in 1972 (Table 1) which divided the tumours into papilloma and grade I, II & III, transitional cell carcinomas (TCC).[8]

A recent classification which has been formulated by World Health Organization Committee on urothelial tumours is called WHO/ISUP Consensus Classification.[9] It has been proposed by the International Society of Urological Pathologists and Canadian Academy of Pathology in 1998. It encompasses various issues regarding terminology of bladder lesions, both neoplastic and preneoplastic. The aim of this classification is to develop a universally accepted system for bladder neoplasia. This classification (Table 2) has been incorporated into the latest WHO histological classification of tumours of the urinary tract .[10]

Evaluation of the most commonly used WHO 1972 Classification system for urothelial tumours has shown significant interobserver variation with varying prognostic implications. [11]

The purpose of this study was to assess the interobserver reproducibility of the WHO/ISUP Consensus Classification 1998 and compare it with that of WHO 1972 Classification.

## MATERIAL AND METHODS

This study was undertaken at Armed Forces Institute of Pathology (AFIP) Rawalpindi from March 2002 to February 2003. Hundred consecutive cases of urothelial (transitional cell) neoplasia diagnosed at Department of Histopathology AFIP during this period were included in the study.

All the slides of these urothelial neoplasms were retrieved. 3-5 u thick sections were recut from paraffin blocks where slides were not available. Four histopathologists (group 1 Iqbal MA & Mamoon N and group 2; Luqman M & Jamal S) participated in the study. The slides were put up to each group separately. The tumours were graded first according to WHO Classification 1972 as papilloma, TCC Grade I, II, and III and later according to WHO/ISUP Consensus Classification 1998 as papilloma, papillary neoplasm of low malignant potential (PNLMP), low grade and high grade urothelial carcinoma by each group independently. The participants were unaware of the previous officially signed out grade of neoplasia.

Interobserver variability was calculated for both classifications and for each grade of both the classifications by using Kappa "k" statistics. Kappa statistics are a measure of overall agreement which do not require any assumption concerning the "correct" diagnosis and which include a correction for the amount of agreement which would be expected by chance alone.[11]

**Table-1: WHO Classification 1972: Morphological features of Transitional Cell Tumors**

| | Hyperplasia (>7 layers) | Superficial cell layer | "Clear" cytoplasm | Pleomor-phism | Nuclear polarization | Nuclear crowding | Chromatin | Mitoses |
|---|---|---|---|---|---|---|---|---|
| Papilloma | None | Preserved | Present | None | Normal | None | Normal | Rare |
| TCC-I* | Variable | Variable | Often absent | Variable | Slightly abnormal | Slight | Fine – regular | Uncommon |
| TCC-II | Variable | Absent | Often absent | Variable | Abnormal | Moderate | Fine – regular | Common |
| TCC-III | None | Absent | Absent; vacuoles common | Prominent | Absent | Moderate | Coarse – usually irregular | Prominent |

**TCC= transitional cell carcinoma – grade I, II, III.*
*From Murphy, W.M.: Current topics in the pathology of bladder cancer. Pathol. Annu.18:1, 1983.*

**Table 2. Histologic features used to classify urothelial papillary lesions according to the scheme proposed by the WHO/ISUP Classification 1998**

| | **Papilloma** | **Papillary neoplasm of low malignant potential** | **Low-grade papillary carcinoma** | **High-grade papillary carcinoma** |
|---|---|---|---|---|
| Papillae | Delicate | Delicate: occasionally fused | Fused, branching and delicate | Fused, branching and delicate |
| Organization of cells | Identical to normal | Polarity identical to normal; any thickness; cohesive | Predominantly ordered, yet minimal crowding and minimal loss of polarity; any thickness; cohesive | Predominantly disordered with frequent loss of polarity; any thickness; often dyscohesive |
| Nuclear size | Identical to normal | May be uniformly enlarged | Enlarged with variation in size | Enlarged with variation in size |
| Nuclear shape | Identical to normal | Elongated, round-oval, uniform | Round-oval; slight variation in shape and contour | Moderate –marked pleomorphism |
| Nuclear chromatin | Fine | Fine | Mild variation within and between cells. | Moderate-marked variation both within and between cells with hyperchromasia |
| Nucleoli | Absent | Absent to inconspicuous | Usually inconspicuous* | Usually present |
| Mitoses | Absent | Rare, basal | Occasional, at any level | Usually frequent, at any level |
| Umbrella cells | Uniformly present | Present | Usually present | May be absent |

*If present, small and regular and not accompanied by other features of high-grade carcinoma.
*(From Epstein JI, Amin MB, Reuter VR, Mostofi FK, and the Bladder Consensus Conference Committee. The World Health Organization/International Society of Urological Pathology Consensus Classification of Urothelial (Transitional Cell) Neoplasms of the Urinary Bladder. Am J Surg Pathol 1998, 22:1435-1448.*

The results were arranged in two tables with the horizontal rows being the categories observed by one group and vertical columns being the categories observed by the second group. The numbers in the diagonals of the table, that is *Oii* are the numbers observed when the two consultants agree. The corresponding numbers expected by chance in the same category are E*ii*. If N is the number of neoplasms that have been classified then we denote *p*observed = ∑*Oii*/N and *p*expected = ∑ E *ii*/N.

The chance corrected observed agreement was calculated as, $k = \frac{p \text{ observed} - p \text{ Expected}}{1 - p \text{ Expected}}$

The overall value of Kappa for more than two categories is defined as weighted average of the values for the individual categories.[12] The value of "k" can range from -1.0 to +1.0. A value of 0 indicates chance agreement only, while a value of 1.0 indicate perfect agreement. A negative value would imply systematic disagreement between observers. It is generally accepted that a value of 0.75 or above reflects excellent agreement, while 0.40-0.75 suggests fair to good agreement and values less than 0.40 mean agreement is poor.[13]

Chi square test was applied to find out the overall statistical difference between the two classifications.

## RESULTS

A comparison of grading of 100 specimens of urothelial neoplasia according to WHO Classification 1972 by two consultants is shown in Table 3 while Table 4 shows the comparison of grades according to WHO/ISUP Consensus Classification 1998.

The Kappa value for WHO classification (1972) calculated from Table 3 was 0.68 signifying good agreement while for WHO/ISUP consensus classification 1998 ( Table 4) it was 0.91 translating as excellent agreement. These kappa values showed that there was better agreement and less variability in WHO/ISUP Consensus Classification 1998 than WHO Classification 1972.

Kappa value for each grade was also calculated as given in Tables 3 & 4. The WHO (1972) classification displayed excellent agreement for I, II and III tumours, but for papilloma the value fell between fair to good. Using WHO/ISUP consensus classification, the value of Kappa for low grade and high grade tumours showed excellent agreement while Kappa value for papilloma and PNLMP showed fair to good agreement.

Statistical significance of difference between the overall kappa values for the two systems was calculated using Chi Square test which showed $p<0.001$. This value illustrates that there is significant difference in the interobserver variability between the two classification systems.

**Table-3: Number of cases allotted different grades by the 2 groups according to WHO Classification 1972 with kappa values**

| **Group 1** | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | **Papilloma** | **TCC grade I** | **TCC grade II** | **TCC grade III** | **Total** |
| **Group2** | | | 0 | 2 | 0 | 0 | 2 |
| | Papilloma | 1 | 1 | 0 | 0 | 0 | 2 |
| | TCC Grade I | 0 | 0 | 6 | 8 | 0 | 14 |
| | TCC Grade II | 0 | 0 | 1 | 37 | 2 | 40 |
| | TCC Grade III | 0 | 0 | 0 | 6 | 36 | 42 |
| | **Total** | 1 | 1 | 9 | 51 | 38 | 100 |
| | **Kappa values** | | 0.25 | 0.79 | 0.82 | 0.82 | |

**TCC : transitional cell carcinoma**

**Table-4: Number of cases allotted different grades by the 2 groups according to WHO / ISUP Consensus Classification 1998 with kappa values**

| **Group 1** | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | Papilloma | PNLMP | LG | HG | Total |
| **Group 2** | | | 0 | 0 | 0 | 0 | 0 |
| | Papilloma | 1 | 1 | 0 | 0 | 0 | 2 |
| | PNLMP | 0 | 0 | 3 | 1 | 0 | 4 |
| | LG | 0 | 0 | 1 | 43 | 0 | 44 |
| | HG | 0 | 0 | 0 | 2 | 48 | 50 |
| | **Total** | 1 | 1 | 4 | 46 | 48 | 100 |
| | **Kappa values** | | 0.67 | 0.75 | 0.92 | 0.96 | |

*PNLMP: papillary neoplasm of low malignant potential ; LG : low grade papillary carcinoma ; HG : high grade papillary carcinoma*

## DISCUSSION

Classification of bladder neoplasms is aimed at separating patients into homogeneous groups whose tumours will have similar natural course and respond similarly to the available therapeutic regimens.[14] Interpretive reproducibility among pathologists has been found to be inversely proportional to the number of criteria and their complexity.[14]

Several groups have examined the variability of hisopathological reporting of bladder neoplasm. Ooms[15] and colleagues examined 67 bladder tumours and found considerably high intraindividual and interindividual inconsistency in grading them according to the WHO Classification. In almost 50% cases the tumours were graded differently at different times by the same pathologist as well. This implied that one pathologist would recommend conservative treatment while another would advise more aggressive treatment based on their different gradings. Tosoni et al[16] found significant interobserver differences in 39% of tumours according to WHO Classification. In another study Busch et al described the reproducibility of grading according to WHO classification by one pathologist on three occasions and showed overall consistency of 80%.[17]

Schapers et al[18] compared the interobserver variability of the WHO grading with a two grade system and found good to excellent reproducibility of the two grade system with a group kappa value of 0.87. WHO/ISUP Consensus Classification 1998 divides papillary tumours into four categories however the carcinomas are categorized into low and high grade. In this way it resembles a two tier classification. Our study revealed excellent agreement according to this classification as most of our cases fell in the two groups of low and high grade carcinoma with a Kappa value of 0.91 while WHO grading system showed good agreement with kappa value of 0.68. It was found easier by both groups to assign carcinomas to a low or high grade according to the WHO/ISUP classification. While using the WHO classification (1972) there was a tendency to assign the lesions to the middle grade (Grade II). This has been observed by many workers not only in relation to bladder carcinomas but other neoplastic lesions as`well. These findings were also statistically significant, like findings of Schapers et al[18]

Kappa values for individual grades of WHO classification revealed that agreement was excellent for grade II & III lesions (0.82) but it was poor for papillomas. Similarly the individual grades of WHO / ISUP consensus classification revealed excellent agreement (0.75 and 0.96) for low grade and high grade papillary carcinoma while agreement was fair to good (0.67) for papillomas and PNLMP. Papillomas constituted only a minority of neoplasms in this study and showed considerable discrepancies in identification. Reproducibility has been reported to be lower for low grade tumours by other workers as well.[19]

The most likely reason of less interobserver variability in the WHO/ISUP classification is probably that the diagnostic criteria for the different grades are more precisely defined in the WHO/ ISUP classification.[20] Another factor is the very small number of benign papillomas and low grade lesions which showed relatively lower individual kappa values in our study. Had they been more frequent, the overall kappa value for both systems would have fallen. This indicates that extra efforts are required on the part of pathologists to gain expertise in identifying these benign and low grade lesions. [19] This has also been highlighted by other workers.[18] Although these lesions are rare which may present some consolation, classifying them correctly is of the utmost importance for the clinician as well as the patient.

Our study revealed less interobserver variability in WHO/ISUP consensus classification as compared to WHO Classification 1972, however other researchers [21] have shown conflicting results. The WHO 1999 Classification including three grades of urothelial carcinomas [22,23] followed by the incorporation of the two-tier system into the latest WHO classification[10] suggests that some form of consensus has been reached however extensive studies are required to evaluate the reproducibility of these new systems as compared to the previous ones along with their efficacy in predicting outcome before one of them can be adopted widely.

## REFERENCES


1. Parkin DM, Pisani P, Ferlay J .Estimates of the worldwide incidence of eighteen major cancers in 1985. Int J Cancer 1993;54(4)594-606.
2. Wingo PA, Tong T, Bolden S. Cancer statistics 1995. Cancer J Clin 1995; 45(1): 8-11.
3. Cheng L, John C, Cheville JC, Neumann RM, Bostwick DG. Natural history of urothelial dysplasia of the bladder. Am J Surg Pathol 1999; 23(4): 443-7.
4. Willet F, Whintmore JR. Summary of all phases of bladder carcinoma. J Urol 1978; 5: 335-8.
5. Cotran RS, Kumar V, Collins T. Robbins Pathologic Basis of Disease. 6th ed. Philadelphia: Saunders, 1999: 1003-04.
6. Broders AC. Epithelioma of the genitourinary organs. Ann Surg 1922; 75: 574-604.
7. Dean AL, Ash JE. Study of bladder tumours in the registry of the American Urological Association. J Urol 1950; 63(4):618-24.
8. Mostofi FK, Sobin LH, Torloni H. Histological typing of urinary bladder tumours. International Classification of tumour (no.10) Geneva, World Health Organization, 1973.
9. Epstein JI, Amin MB, Reuter VR, Mostofi FK. The World Health Organization/ International Society of Urological

Pathology Consensus Classification for urothelial (transitional cell) neoplasms of the urinary bladder. Am J Surg Pathol 1998; 22:1435-8.
10. Eble JN, Sauter G, Epstein JI, Sesterhenn IA. World Health Organization Classification of Tumours Pathology and Genetics of Tumours of The Urinary system and Male Genital Organs. WHO Geneva (2004).
11. Cohen JA. A coefficient of agreement for nominal scales. Educational Psychological Measurements 1960;20 (1):37-47.
12. Fleiss JL. Statistical methods for rates and proportions. 2nd ed, New York: John Wiley, 1981: 135-7
13. Landis JR, Koch GG. The measurement observer agreement for categorical data. Biometrics 1977; 33: 159-74.
14. Murphy WM, Grignon DJ ,Perlman EJ (eds) Tumours of kidney , bladder and related urinary structures . AFIP Atlas of Tumour Pathology. Fourth Series Fascicle Washington DC 2004,241- 361
15. Ooms ECM, Anderson WAD, Alons CL, Boon ME, Veldhuizen RW. Analysis of the performance of pathologists in the grading of bladder tumours. Hum Pathol 1983; 14:140-3.
16. Tosoni I, Wagner U, Sauter G, Egi G, Knonagel H, Alund G, et al. Clinical significance of interobserver differences in the staging and grading of superficial bladder cancer. BJU International 2000;85:48-53.
17. Busch C, Engberg A, Norlen BJ, Stenkvist B. Malignancy grading of epithelial bladder tumours. Reproducibility of grading and comparison between forceps biopsy, aspiration biopsy and exfoliative cytology. Scand J Urol Nephrol 1977; 11: 43-8.
18. Schapers RF, Pauwels RP, Wijnen JT, Arends JW, Thunnissen FB, Coebergh JW, et al. A simplified grading method of transitional cell carcinoma of the urinary bladder: reproducibility, clinical significance and comparison with other prognostic parameters. Br J Urol 1994;73(6):625-31.
19. Yorukoglu K, Tuna B, Dikicioglu E, Duzcan E, Isisag A, Sen S et al. Reproducibility of the 1998 World Health Organization / International Society of Urologic Pathology classification of papillary urothelial neoplasms of the urinary bladder. Virchows Arch 2000;443 (6) :734-40
20. Epstein JL. The new World Health Organization / International Society of Urologic Pathology (WHO/ISUP) classification for TA, T1 bladder tumours: is it an improvement? Crit Rev Oncol Hematol 2003;47(2):83-9.
21. Mikuz G. The reliability and reproducibility of the different classifications of bladder cancer. In: Hauptmann S. Dietel M . Sobinho-Simoes M eds. Surg Pathology update 2001. 18th European Congress of Pathology. Berlin: ABW Wissenschaftsverlag 2001: 114-5.
22. Busch C, Algab F. The WHO /ISUP 1998 and 1999 systems for malignancy grading of bladder cancer. Scientific Foundation and translation to one another and previous systems. Virchows Arch 2002;441(2); 105-8.
23. Helpap B. New WHO classification of urothelial carcinoma of the urinary bladder. Verh Dtsch Ges Pathol 2002;86;57-6

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