

**How to Cite:**

Jain, M., Patel, K., & Chauhan, Y. (2022). The Paris system in reporting urinary cytology and correlating with follow up histopathological evaluation, in tertiary care hospital. *International Journal of Health Sciences*, 6(S10), 573–583.  
<https://doi.org/10.53730/ijhs.v6nS10.13547>

## **The Paris system in reporting urinary cytology and correlating with follow up histopathological evaluation, in tertiary care hospital**

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**Abstract**--Introduction: Away from diagnostic importance, urinary tract endoscopy is a painful, expensive and time consuming procedure. Now a time, The Paris System for Reporting Urinary Cytology (TPSRUC) has lead to prime changes in the perspective of assessment in urine cytology and pattern of reporting. Our focus in this study was to evaluate the impact of implementing The Paris system in reporting urinary cytology and correlating with follow up histopathological evaluation. Patients & Methods: It is a Retrospective study of 6 months duration, from January 2021 to June 2021 using 156 urine samples in Cytology section, Department of pathology at Dhiraj hospital Waghodia. All freshly collected urine specimens were centrifuged, prepared as thin slides fixed with methanol and stained with Hematoxylin & eosin (H&E) and Papanicolaou stain then evaluated under light microscopy. Results: In total, 156 cytology specimens the sample was composed of 90 (58%) men and 66 (42%) women (the ratio of men to women was 1.4:1). Out of total 156 samples Majority of the samples were negative for HGUC (118 cases, 76.1%). 22 cases (13.9%) of AUC, 4 cases of SHGUC (2.7%), 10 cases (6.1%) of HGUC, 1 case (0.6%) of other malignant neoplasms 1 case (0.6%) was suboptimal for evaluation due to acellular or severe paucicellular specimens. None of our samples were diagnosed with

LGUN. Conclusion: Urine cytology is using TPS system is helpful in decreasing the report of atypical urothelial cells category that are more strongly associated with HGUC and providing clear information to clinicians. TPS is explaining more aggressive investigations of patients who receive an AUC as diagnosis.

**Keywords**--Paris System for Reporting Urinary Cytology (PSRUC), atypical, cytology, urine.

**Introduction:**

Cancer of the bladder is also known as urological cancer, urinary bladder cancer or urothelial carcinoma, is the 10th most common cancer in the world and it's incidence is steadily rising worldwide (1,2). Transitional epithelial cells lining the urinary bladder and urinary tract, known as urothelial cells, accommodate the volume of urine produced by flattening under pressure. The bladder is also lined with smooth muscle that can relax to accommodate greater volumes, as well as contract under voluntary or reflex control to expel urine down the urethra and out of the body [3]. There are two main types of urothelial carcinoma (UC) are papillary urothelial carcinoma (pTa) and "flat" urothelial carcinoma (pTis), also called as noninvasive carcinoma in situ. Approximately 75% to 80% of urothelial carcinomas are papillary and approximately 20% to 25% are Carcinoma in situ (CIS). Papillary urothelial carcinoma is often slow growing and it is easily treatable rather than other types of urinary bladder cancer. The prognosis of papillary UCs is generally good. CIS is aggressive and it tends to progress towards muscle invasive cancers.

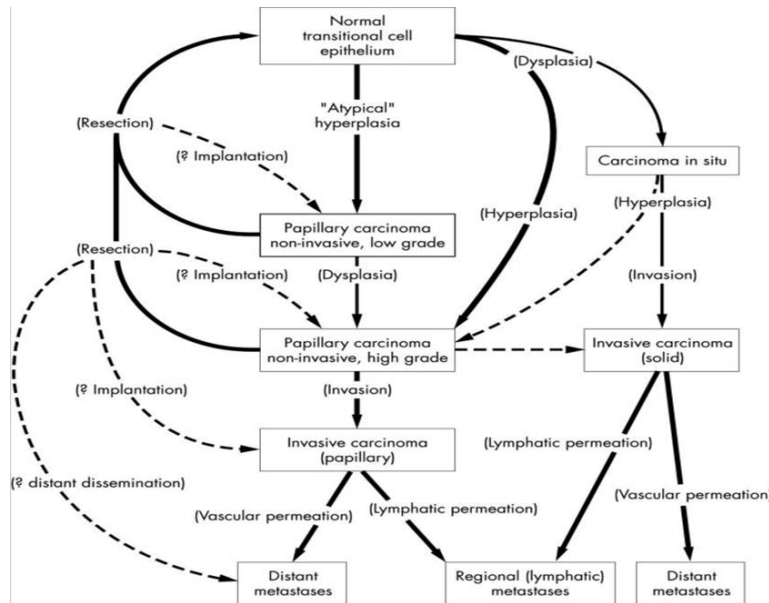


Figure 1. Morphological pathways for bladder tumour classification and grading. Reproduced, with permission, from Jones *et al.*(4)

Urothelial carcinoma tumorigenesis is a multistep progression. Papillary Urothelial carcinomas are thought to be arised from areas of urothelial hyperplasia or from urothelial papillomas. Although most of the papillary tumors are low-grade tumors that have little tendency to progress to invasive tumors, a small proportion are high grade tumors that have significant possibility to progress into invasive urothelial carcinoma. Most invasive urothelial carcinoma is tends to arise through the following sequence of events: normal urothelium to dysplasia to carcinoma in situ to invasive cancer. Urothelial carcinoma can be diagnosed by several ways together with biopsy, cystoscopic evaluation, urine biomarkers and urine cytology. Urine cytology can best detect larger, more-aggressive and high grade urinary tract cancers. It might not detect small urinary tract cancers that grow more slowly. The Paris System (TPS) which we are using for Reporting Urinary Cyto-pathology was conceived during the International Academy of Cytology Congress which held in Paris on 2013,May and was officially released in 2016 (5,6)

- TPS is simple, safe, and cost-effective method that may expose hidden urothelial carcinomas.
- It is primarily used for diagnosis for symptomatic patients.
- Detection of cancers in high risks patients
- It is also useful in follow-up patients with history of urinary tract neoplasia.

The prime purpose of the Paris system is to detect high grade urothelial carcinomas (5). The diagnostic categories of The Paris system for reporting urine cytology(TPSRUC) are negative for malignancy, low-grade urothelial neoplasm (LGUN), atypical urothelial cells (AUCs), suspicious for high grade urothelial carcinomas (SHGUC), High grade urothelial carcinoma (HGUC) and other malignancies. A consequential purpose of the TPSRUC was to replace the existing analytical category of “atypical urothelial cells” with a more reproducible and clinically significant model [7]. Our institute has been utilizing TPSRUC in urine cytology screening and diagnoses. This study offers an appraisal of impact of The Paris system in reporting urine cytology system and examines the correlations between cyto-histopathological diagnosis.

### **Materials and Methods:**

This was a retrospective cross sectional study. All cytology urine specimens obtained from January 2021 to June 2021 using 156 urine samples in Cytology section, Department of Pathology at Dhiraj hospital Waghodia. For each patient specimen, the patient’s identity, age, gender, specimen collection date, Type of specimen received (Voided and instrumental urine), and type of procedure (Biopsy, transurethral resection of bladder tumor, and organ resection) and surgical histopathological specimen were recorded. The data were collected anonymously to keep patient confidentiality. All fresh urine specimens obtained in sterile urine containers .All specimens were centrifuged at ~3000 RPM for 10 min, prepared 2 thick and 2 thin slides with cell button, were fixed with methanol and stained 2 slides with Hematoxylin & eosin (H&E) stain and 2 slides with Papanicolaou stain. The slides were evaluated under light microscopy by consultant pathologists and reported by using The Paris system of reporting urine cytology. The categories for TPS are NHGUC, AUC, SHGUC, HGUC, LGUN, other

malignant neoplasms, and non-diagnostic. The Non diagnostic category was applied to those samples insufficient for cytological diagnosis. For each specimen, details of any subsequent specimen, laboratory reports and previous reports for the same patient in subsequent year were also obtained. Received surgical Histopathological specimen was categorized as:

- Negative for malignancy (i.e., non-neoplastic tissue, infection, cystitis and reactive changes)
- HGUC (i.e. urothelial carcinoma in situ, invasive, and noninvasive HGUC),
- LGUN (i.e. papillary urothelial neoplasm of low malignant potential, low-grade urothelial carcinoma and papillomas)
- Non-urothelial neoplasia.

All the cases of cytological and histological finding discordance were re-reviewed by consultant pathologist. By using The Paris system in urine cytology sensitivity, specificity, accuracy and risk of high grade malignancy were determined.

## **Results:**

### **Clinical data and specimen type**

We collected total, 156 urine cytology specimens. The types of urine specimen included 119 (76.2%) from voided urine sample, 33 (21.1%) instrumented urine sample, and 4 (2.56%) from unspecified sites of collection. Males were slightly predominated. In our study the sample was of 90 (58%) men and 66 (42%) women. The men to women ratio were 1.40:1. The mean age of patient was 66 years old. (Range: 15–96 years old).

### **Cytological diagnosis**

Out of total 156 samples Majority of the samples were negative for HGUC (118 cases, 76.1%) and the remaining cases were diagnosed as follows: 2 cases (13.9%) of AUC, 4 cases of SHGUC (2.7%), 10 cases (6.1%) of HGUC, 1 case (0.6%) of other malignant neoplasms 1 case (0.6%) was suboptimal for evaluation due to acellular or severe paucicellular specimens. None of our samples were diagnosed with LGUN.

### **Histodiagnosis and histo-cytological correlations**

In total 156 cases (20% of cytology specimens) provided a subsequent histological sample after cytology diagnosis. The histology diagnoses in these cases were HGUC, negative for neoplasm, AUC, SHGUC and other malignant neoplasms, in 7(21.8%), 16(50%), 3(9.37), 5(15.62%), and 1(3.12%) cases, respectively. Based on TPSRUC diagnostic categories, the cytology specimens of these 32 cases were categorized into NHGUC, AUC, SHGUC, HGUC, and other neoplasms in 15(46.8%), 6 (18.75), 2(6.25%), 8 (25%), and 1 (3.12%) cases, respectively. Only 0.4% cases were deemed to non-diagnostic.

Table-1,2  
Urine cytology specimens (diagnostic categories, age, gender and specimen type)

Table: 1

Cytologic Diagnostic Category	ND	NHGUC	AUC	SHGUC	HGUC	Other neoplasm	Total
Case	1	118	22	4	10	1	156
Age	36-85 (61)	18-96 (65)	15-96 (66)	28-89 (69)	28-89 (69)	39-78 (61)	3-96 (66)
Gender (M:F)	0:1	68:50	13:9	2:2	6:4	1:0	90:66
ND: NON DIAGNOSTIC							

Table: 2

Type of specimen	ND	NHGUC	AUC	SHGUC	HGUC	Other Neoplasm	Total
Voided	0	92	17	2	7	1	119
Instrument	1	22	5	2	3	0	33
Unspecified	-	4	-	-	-	-	4
ND: NON DIAGNOSTIC							

Table 3  
Correlations between urine cytology categories (based on TPSRUC) and subsequent surgical samples

Cytologic diagnostic category	ND	NHGUC	AUC	SHGUC	HGUC	Other neoplasm	Total
Case, n%	0	15(46.8%)	6 (18.75%)	2 (6.25%)	8 (25%)	1 (3.12%)	32
Negativ for neoplasm	-	9	3	1	2	1	16 (50%)
SHGUC	-	2	1	-	2	-	5 (15.6%)
HGUC	-	3	-	-	4	-	7 (21.8%)
AUC	-	1	1	1	-	-	3 (9.37%)
Other Malignant lesion	-	-	1	-	-	-	1 (3.12%)
ND: NON DIAGNOSTIC							

**Figures**

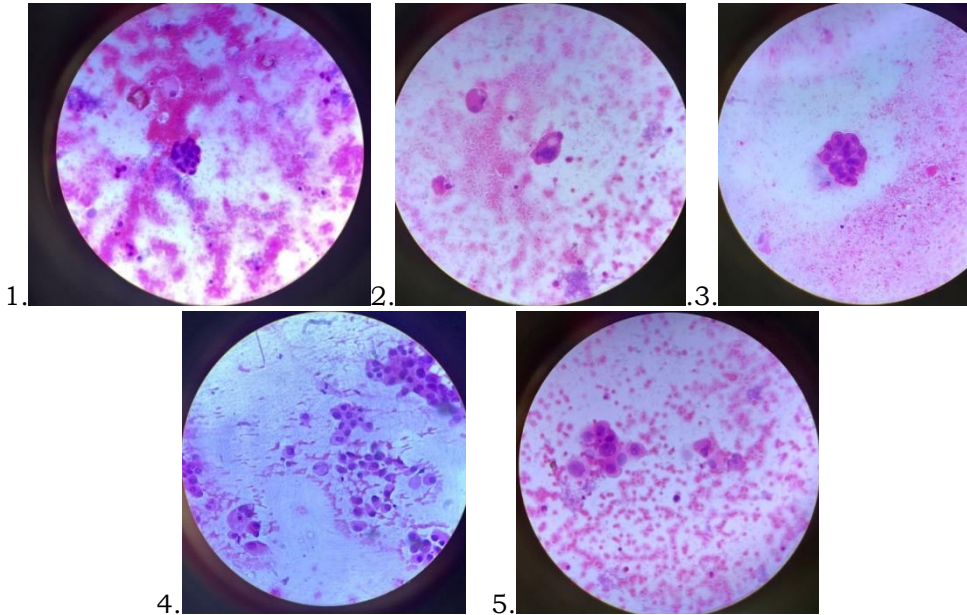


Fig.1. 10xPF- Contamination – inadequate for reporting; Fig.2 & 3: 40xPF- Low cellularity; Fig.4 & 5: 100xHPF - Adequate cellularity

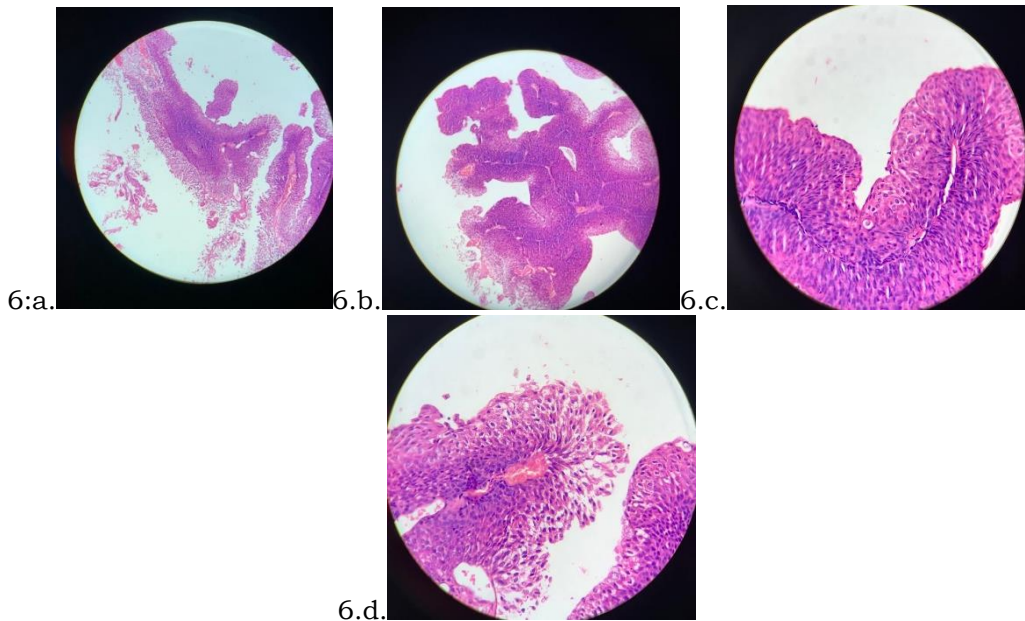


Fig 6. (6.a. 4xPF; 6.b. 10xPF; 6.c. 40xHPF; 6.d. 40xHPF) - Low Grade Urothelial Carcinoma

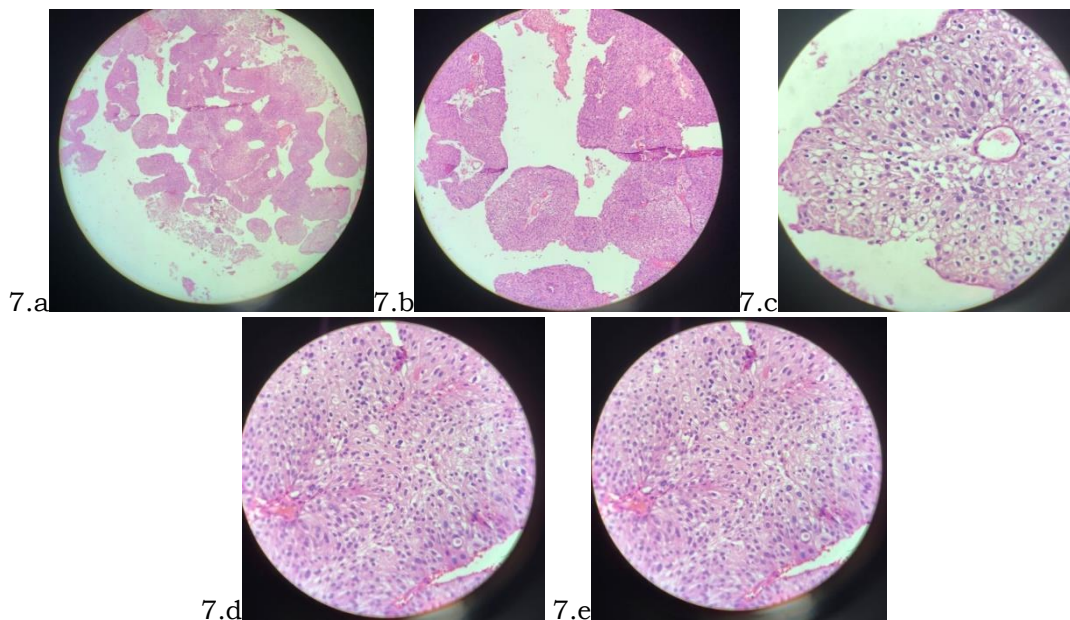


Fig 7. (7.a. 4xPF; 7.b. 10xPF; 7.c. 40xHPF; 7.d. 40xHPF) - High Grade Urothelial Carcinoma,

## Discussion

Urine cytology is an important test for screening, surveillance and maintenance of newly developed, recurrence and high risk urothelial carcinoma which includes bladder, kidney, prostate, ureter and urethra cancers. The main goal of using The Paris system is to diagnose clinically significant urothelial carcinoma, mainly high grade urothelial carcinoma. Before reporting of urine cytology the main things which should be in consideration is adequacy of received urine specimen because it can be the main cause of discrepancy in reporting of urine cytology when two separate pathologists are reporting the different samples of the same patient. A healthy distended urinary bladder has maximum approximate capacity is 650 ml. The average urothelial cells have approximate size of 20 micron in diameter. The urothelium is about five cells thick, so the total number of urothelial cells lining the bladder is on the order of  $10^8$  -  $10^9$  cells (8). That is why; a highly cellular urine specimen contains very less numbers of the urothelial cells lining the bladder and possibility of may or may not have cellularity or abnormal/atypical cells.

Adequacy of urine specimen in reporting includes collection type (voided or instrument urine), cellularity, volume and procedure used during slide preparation. Urine is a mixture of non solute particles like cells, crystals, cast, contamination, cells remnants. We should not use first stream of urine specimen and first morning sample, there is high chances of false reporting because it shows more likely amorphous material and degenerated cells because of concentrated specimen. As we compared voided urine specimen, instrumented specimen (bladder washing) show high cellularity and less contamination. We reported unsatisfactory or non-diagnostic when specimen shows highly

inflammatory, RBCs or amorphous material background obscuring urothelial cells. When slide shows 10-20 cells, well preserved, well visualized per 10 high power field is we called as satisfactory for diagnostic urinary cytology. If it is less than 10 cells/HPF called it as an unsatisfactory specimen. In voided urine specimen cellularity criteria is not defined as voided specimen usually has low cellularity so we confirmed adequacy with one repeated urine specimen then interpret confirmed report.

After TPSRUC execution, multiple previous studies have confirmed advancement and approach to diagnostic efficiency with TPSRUC compared to other traditional reporting systems. The current study evaluated that the Paris system for reporting urine cytology improved the result of urine cytology. It decreases the rate of atypical urothelial cell diagnosis while increasing the sensitivity significantly towards the diagnosis of High grade urothelial carcinoma. Several studies also reported the same findings (9-14). This study evaluated The Paris system in urine cytology in 90 cases which presented with painless hematuria. The median age of patients with urothelial carcinomas was 66 years and was more prevalent in males as seen in other studies. (15-18)

Our conclusion also put forward that the quantitative criterion for categorizing smears with severely atypical cells present with more than 5 and less than 10 cells suggested as SHGUC and equal to or more than 10 numbers of cells as HGUC, as recommended by The Paris system to distinguish SHGUC and HGUC, are highly valid. Utility The Paris system also resulted in a decrease in the proportion of cases diagnosed as atypical urothelial cell from 43% to 31%. Among the Atypical urothelial cells cases, the proportion of histologically confirmed high grade urothelial carcinoma cases rose (75% to 80%), as did the proportion of low-grade urothelial neoplasm (57% to 71%). Sharda rai et al.[16] (19) the cytology of the urine specimen is reported as HGUC or SHGUC by The Paris system, there is very high probability of malignancy, whereas a negative result does not always confirm the absence of malignancy of the reported specimen.

The predictive value for HGUC on histological specimens was significantly increased for the suspicious category by using TPS criteria. However, connection of the "atypia" category with subsequent HGUC was decreased, because a separation of cases with cytologic atypia of cells was upgraded to the SHGUC category. These findings suggest that former to implementing TPS in our institution, a wide range of "atypical" features, including benign/reactive to somewhat worrisome for an underlying malignancy, were used to place into atypical urothelial cell category. By applying TPS criteria, a significant segment of these cases were assigned to benign or higher-grade categories, which showed excellent correlation with the follow-up histology, therefore indicating better morphologic criteria were clear by TPS.

Our data showed that the category of HGUC from The Paris reporting systems has high predictive value for reporting HGUC (20,21)The observed difference probably reflects institutional variation between diagnostic criteria for HGUC before introduction of TPS. TPS showed slightly better sensitivity and NPV, which is an important finding because classifying more cases as NHGUC by TPS may raise concern about the sensitivity of urinary tract cytology as a screening test.

TPS showed significantly improved specificity, PPV and diagnostic accuracy for detecting HGUC; therefore we concluded it improves the diagnostic accuracy and overall performance of urine cytology. We observed acceptable interobserver agreement. Two cyto-pathologists who reviewed the urine samples independently agreed on 85% of the cases by applying the strict criteria of TPS. In the majority of the cases with different interpretations, the diagnoses did not show a major discrepancy and agreed on the benign or malignant nature of the pathology, which would result in a low impact on clinical management. Somaye Zare et al (19) reported high interobserver variability, including major discrepancies with high clinical impact, but our study did not show that.

### **Conclusion**

The Paris system for reporting urine cytology is useful for reporting urine cytology. As by using the TPS system decreased the cases of AUC and raises the reporting cases of high grade urothelial carcinoma. TPS is also useful for follow up the patient who has previous history of urothelial carcinoma. It is less invasive, cost effective and time saving method. As it has high predictive values for HGUC so it is also reliable for treatment purpose. Only the drawback is high observation and practice is required for using this reporting system.

### **Abbreviations**

PSRUC	: Paris System for Reporting Urinary Cytology
CIS	: Carcinoma in situ
UC	: Urothelial carcinoma
TPS	: The Paris System
LGUC	: Low-grade urothelial carcinoma
HGUC	: High-grade urothelial carcinoma
AUC	: Atypical urothelial cells
NPV	: Negative predictive value
PPV	: Positive predictive value
TURBT	: Transurethral resection of bladder tumor
SHGUC	: Suspicious for high-grade urothelial carcinoma
NHGUC	: Negative for high-grade urothelial carcinoma
BC	: Bladder cancer
NMIBC	: Non-muscle-invasive bladder cancer

### **Statement of ethics**

Approval taken from institute ethics committee (SVIEC, Piparia, Vadodara).

### **Conflict of interest**

The authors made no disclosures.

### **Funding Sources**

The authors received no financial support for the research, authorship, and/or publication of this article

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