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Original Research Article

Implementation of the Paris system versus institutional diagnosis in the performance of urinary cytology: A 5 years correlative study of 74 cases

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ARTICLE INFO

Article history:
Received 21-06-2019
Accepted 23-07-2019
Available online 01-10-2019

Keywords:
Atypical cells
Urine cytology
The Paris System
High-gradeurothelial carcinoma
Uothelial neoplasms

ABSTRACT

Introduction: Urine cytology used for diagnosing high-grade urothelial carcinoma (HGUC), but plagued by low sensitivity and wide inter-observer variability mainly ascribed to the lack of an established template of reporting. We assessed the performance of urine cytology by comparing the Paris System with our current institutional system. This study is developed to identify the prevalence of various cytological categories and their association with a subsequent diagnosis of high-grade urothelial carcinoma.

Materials and Methods : A total of seventy four urine cytological specimens were studied which have follow up biopsy with histological correlation was done to categorize: benign, atypical urothelial cells (AUCs), suspicious for high-grade urothelial carcinoma (SHGUC), and high-grade urothelial carcinoma (HGUC). Original cytological diagnoses were recorded.

Results: Males outnumbered females with a mean age of 57.4 years (range 21-86) (46 M and 28 F) with no statistical significance among the age groups and between male and female genders. By applying TPS, number of cases assigned to AUC category are very few (7 cases out of 74 with 9.45. Using the TPS resulted in a higher number of low-grade carcinomas assigned to the benign rather than the AUC category. LGUN category includes all low grade urothelial neoplasms of urinary tract, such as LGUC and PUN of uncertain malignant potential.

According to institute diagnosis categories for urine cytology, there were 2 cases shown negatives, 16 cases shown Atypical/suspicious, 21 cases shown LG papillomas, and 35 cases shown HGUC. In negative group; out of 2 cases, 2 cases were papilloma. In HGUC group, out of 35 cases, 27 cases were turned out to be HGUC with 77.14%. In HGUC group, out of 35 cases, 8 cases were turned out to be LGUP with 29.62%.

Conclusion: The TPS seems to improve the performance of urine cytology by limiting the AUC category to cases that are more strongly associated with HGUC. This is the first inclusive attempt at standardizing urinary cytology.

1. Introduction

Data from the Indian cancer registry reported bladder cancer to be the ninth commonest cancer in men. Male preponderance is more pronounced in India (approximate male: female ratio of 8.6:1) than in the Western population (3:1 to 5:1), which could likely be attributed to decreased exposure to putative risk factors such as smoking and industrial carcinogen among Indian women. However, the stage-adjusted survival is worse in women than in men. [1]

For any reporting system to be successful and be applied in daily practice, it must be based on consensus, evidence, inclusion, acceptance, and understanding.

Transitional cell carcinoma is the most common histological type diagnosed in over 95% of urinary bladder (UB) cancer patients in India. Almost all patients seek medical attention due to painless haematuria, and approximately half of UB cancer patients have high-grade tumours at the time of diagnosis. [2]

Despite the grim facts, the silver lining in UB cancer management is the ease of screening for new and recurrent high-grade tumours, by way of an inexpensive and

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https://doi.org/10.18231/j.achr.2019.037
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non-invasive specimen available in cytology practice, ie the voided urine sample. The main goal of urinary cytology is the detection of urothelial carcinoma that is clinically significant, namely high-grade urothelial carcinoma (HGUC). Therefore, the understanding of this disease, and particularly its pathogenesis, was crucial in the process of creating The Paris System for Reporting Urinary Cytology.

For urologists, understanding the diagnostic criteria, their clinical implications, and the limitations of TPS is essential if they are to utilize urine cytology and noninvasive ancillary tests in a thoughtful and practical manner.

The Paris System (TPS) working group proposed such a template at the 2013 International Congress of Cytology, replete with objective criteria for categorising specimens into one of the seven categories: non-diagnostic, negative for HGUC, atypical urothelial cells, suspicious for HGUC, HGUC, low-grade urothelial neoplasm and others (including non-malignant entities).[3–5]

This study was undertaken to determine the impact of TPS criteria and institutional criteria in the morphological interpretation of urine samples.

2. Materials and Methods

2.1. This is a retrospective study of 5 years duration from 2014 to 2018

2.2. Urine cytology

A total of 74 cases of urine specimens were studied and a ll the patients had also undergone follow-up cystoscopy and biopsy. May-Grunwald-Giemsa stained smears were prepared from cytocentrifuged urine specimens were retrieved. The original highest category assigned to each sample was noted, which included unsatisfactory, negative, atypical or positive for malignancy. The cytological features were re-assessed according to the criteria laid down by TPS by different cytopathologists together who were blinded to the final biopsy diagnosis and each specimen was reclassified into one of the seven TPS categories. We re-examined every sample from a patient as per TPS criteria, but only the highest " original " and " re-classified TPS " categories were included in the results.

In comparision to our institutional basis, the paris system (TPS) was also applied to catogerize to identify distribution of benign, atypical urothelial cells (AUCs), suspicious for high[jk1] -grade urothelial carcinoma (SHGUC), and high-gradeurothelial carcinoma (HGUC). A urine sample was required to contain non-superficial and nondegenerated urothelial cells with a nucleocytoplasmic (N/C) ratio of at least 0.5 and the presence of any one of the following three criteria to qualify as AUC, ie hyperchromasia, irregular, clumped chromatin and nuclear membrane irregularity. A sample containing very few cells exhibiting hyperchromasia, an N/C ratio of at least 0.7 and irregular clumped chromatin, or irregular nuclear membranes mandated a diagnosis of at least suspicious for HGUC (SHGUC). A definite HGUC category was assigned when a minimum of 5 to 10 severely abnormal cells with an N/C ratio of $\geq$0.7, in addition to all the minor criteria, were present. A diagnosis of LGUN could only be made if three-dimensional papillary clusters of urothelial cells were observed.[6–8]

The cytological diagnosis was correlated with the final histological diagnosis.

Chi-square statistical analysis was carried out to correlate the TPS system with institutional cytology and biopsy examination. P value set for 0.05 for statistical significance. Statistical analysis performed using SPSS ver. 16.0 (IBM, US) software.

3. Result

Males outnumbered females with a mean age of 57.4 years (range 2 1-86)(46 M and 28 F). There was no statistical significance observed between age groups of male and female genders.

According to institute diagnosis categories for urine cytology, there were 2 cases shown negatives, 16 cases shown Atypical/suspicious, 21 cases shown LG papillomas, and 35 cases shown HGUC.

In negative group ; out of 2 cases, 2 cases were papilloma.

Therefore, the cytology versus histopathology correlation observed as 100%.

In atypical group, out of 16 cases, 12 cases were suspicious of HGUL i.e. 12/16 (75%) of sensitivity. In atypical group, out of 16 cases, 2 cases suspicious of LGUP=2/16=12.5%.

In LGP group, out of 21 cases, 9 cases were turned out to be LGUN with 42.85%. In LGP group, out of 21 cases, 3 cases were turned out to be HGUC with 14.28%. In LGP group, out of 21 cases, 6 cases were turned out to be PUNLMP with 28.57%. In LGP group, out of 21 cases, 3 cases were turned out to be PAPILLOMA with 14.28%.

In HGUC group, out of 35 cases, 27 cases were turned out to be HGUC with 77.14%. In HGUC group, out of 35 cases, 8 cases were turned out to be LGUP with 29.62%.

3.1. Implementation of the paris system(TPS):

By applying TPS, 74 cases were reviewed and categorized as following.

3.2. In NHGUC category

2 cases out of 6 were LGUP with 33.33%. 4 cases out of 6 were PAPILLOMA with 66.66%.

None of the cases diagnosed as NHGUC by applying TPS turned out to be HGUC. Therefore, TPS is working well in defining HGUC,2 cases of LGUP were included in this

Table 1: Crosstabulation-institutional cytology report X the pairs system cytology report.

			The Pairs System Cytology Report					Total
			AUC	HGUC	LGUN	NHGUC	SHGUC	
Institutional Cytology Report	Atypical/ Suspicious for Malignancy	Count	4	5	0	0	7	16
		% within Institutional Cytology Report	25.0%	31.3%	0.0%	0.0%	43.8%	100.0%
		% within THE Pairs System Cytology Report	57.1%	19.2%	0.0%	0.0%	38.9%	21.6%
	HGUC	Count	0	20	7	0	8	35
		% within Institutional Cytology Report	0.0%	57.1%	20.0%	0.0%	22.9%	100.0%
		% within THE Pairs System Cytology Report	0.0%	76.9%	41.2%	0.0%	44.4%	47.3%
	LGP	Count	2	1	10	5	3	21
		% within Institutional Cytology Report	9.5%	4.8%	47.6%	23.8%	14.3%	100.0%
		% within THE Pairs System Cytology Report	28.6%	3.8%	58.8%	83.3%	16.7%	28.4%
	NEM	Count	1	0	0	1	0	2
		% within Institutional Cytology Report	50.0%	0.0%	0.0%	50.0%	0.0%	100.0%
		% within THE Pairs System Cytology Report	14.3%	0.0%	0.0%	16.7%	0.0%	2.7%
Total		Count	7	26	17	6	18	74
		% within Institutional Cytology Report	9.5%	35.1%	23.0%	8.1%	24.3%	100.0%
		% within THE Pairs System Cytology Report	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%

Table 2: Chi-square tests [institutionalcytology report and the pairs system cytology report

	Value	df	P Value
Pearson Chi-Square	50.522a	12	<0.0001 VHS
Likelihood Ratio	56.495	12	0.000
N of Valid Cases	74		

a: 14 cells (70.0%) have expected count less than 5. The minimum expected count is 0.16
VHS: Very high significant

group .4 cases of PAPILLOMA were included in this group.

Aim of NHGUC is only to rule out HGUC otherwise it identifies all other cells like superficial squanous cells, benign glangular cells benign urothelial tissue fragments, reactive urothelial cells/umbrella cells.

In AUL catogery; out of 7 cases, 2 cases turned out to be LGUP with 28%. Out of 7 cases, 4 turned out to be PUNLMP with 57.14%. Out of 7 cases, 1 case turned out to be PAPILLOMA.

But as compared to conventional system, (16 cases out of 74 with 21.62%).

By applying TPS, n umber of cases assigned to AUC category are very few (7 cases out of 74 with 9.45%).

Therefore, a mbiguity has been decreased. None of AUC turned to HGUC.

In SHGUC category; 16 cases out of 18 were turned out to be HGUC with 88.88%. 1 case out of 18 were turned out to be LGP with 5.55%. 16 cases out of 18 were turned out to be PUNLMP with 5.55%.

In HGUL category; 26 cases out of 26 with 100% of HGUC. No case came under PAPILLOMA, PUNLMP, and LGUP.

In LGUN category; 14 cases out of 17 were LGUP with 82.35%. 3 cases out of 17 were PUNLMP with 17.64%. None were turned out to be HGUC/PAPILLOMA.

LGUN category includes all low grade urothelial neoplasm s of urinary tract, such as LGUC and PUN of uncertain malignant potential. True papillary fragments are seen with no features of HGUC.

4. Discussion

We assessed the performance of urine cytology using the Paris System for Reporting Urine Cytology (PSRUC) in

Table 3: Crosstabulation- institutionalcytology report X biopsy report institute

			BIOPSY REPORT INSTITUTE				Total
			HGUC	LGUP	PAPILLOMA	PUNLMP	
Institutional Cytology Report	Atypical/ Suspicious for Maligancy	Count	12	2	0	2	16
		% within Institutional Cytology Report	75.0%	12.5%	0.0%	12.5%	100.0%
		% within Biopsy Report Institute	28.6%	10.5%	0.0%	25.0%	21.6%
	HGUC	Count	27	8	0	0	35
		% within Institutional Cytology Report	77.1%	22.9%	0.0%	0.0%	100.0%
		% within Biopsy Report Institute	64.3%	42.1%	0.0%	0.0%	47.3%
	LGP	Count	3	9	3	6	21
		% within Institutional Cytology Report	14.3%	42.9%	14.3%	28.6%	100.0%
		% within Biopsy Report Institute	7.1%	47.4%	60.0%	75.0%	28.4%
	NEM	Count	0	0	2	0	2
		% within Institutional Cytology Report	0.0%	0.0%	100.0%	0.0%	100.0%
		% within Biopsy Report Institute	0.0%	0.0%	40.0%	0.0%	2.7%
Total		Count	42	19	5	8	74
		% within Institutional Cytology Report	56.8%	25.7%	6.8%	10.8%	100.0%
		% within Biopsy Report Institute	100.0%	100.0%	100.0%	100.0%	100.0%

Table 4: Chi-squaretests [institutionalcytology report and biopsy report institute]

	Value	df	P Value
Pearson Chi-Square	56.541a	9	<0.0001 VHS
Likelihood Ratio	46.980	9	0.000
N of Valid Cases	74		

a. 11 cells (68.8%) have expected count less than 5. The minimum expected count is 0.14.

Table 5: Crosstabulation- biopsy report institute X the pairs system cytology report

			THE PAIRS SYSTEM CYTOLOGY REPORT					Total
			AUC	HGUC	LGUN	NHGUC	SHGUC	
Biopsy Report Institute	HGUC	Count	0	26	0	0	16	42
		% within Biopsy Report Institute	0.0%	61.9%	0.0%	0.0%	38.1%	100.0%
		% within The Pairs System Cytology Report	0.0%	100.0%	0.0%	0.0%	88.9%	56.8%
	LGUP	Count	2	0	14	2	1	19
		% within Biopsy Report Institute	10.5%	0.0%	73.7%	10.5%	5.3%	100.0%
		% within The Pairs System Cytology Report	28.6%	0.0%	82.4%	33.3%	5.6%	25.7%
	PAPILLOMA	Count	1	0	0	4	0	5
		% within Biopsy Report Institute	20.0%	0.0%	0.0%	80.0%	0.0%	100.0%
		% within The Pairs System Cytology Report	14.3%	0.0%	0.0%	66.7%	0.0%	6.8%
	PUNLMP	Count	4	0	3	0	1	8
		% within Biopsy Report Institute	50.0%	0.0%	37.5%	0.0%	12.5%	100.0%
		% within The Pairs System Cytology Report	57.1%	0.0%	17.6%	0.0%	5.6%	10.8%
Total		Count	7	26	17	6	18	74
		% within Biopsy Report Institute	9.5%	35.1%	23.0%	8.1%	24.3%	100.0%
		% within The Pairs System Cytology Report	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%

Table 6: Chi-squaretests [biopsy report institute and tps cytology report]

	Value	df	P Value
Pearson Chi-Square	114.945a	12	<0.0001 VHS
Likelihood Ratio	109.591	12	0.000
N of Valid Cases	74		

a. 16 cells (80.0%) have expected count less than 5. The minimum expected count is 0.41.

comparison to our current system.

Even in carcinomas that are not seen by cystoscopy (i e, occult carcinomas), a positive urine cytology diagnosis is a clinically meaningful result even in the absence of tissue confirmation.[5,6]

Several investigators attempted to address this issue by proposing various classification systems for urine cytology reporting. Dr Papanicolaou (1947) pioneered it which was followed by classification systems proposed by Dr Leopold G. Koss (1978) , Dr Murphy (1984), Drs Ooms and Veldhuizen (1993) and, more recently, the recommendations by the Papanicolaou Society of Cytopathology published in 2004 and the John Hopkins template for reporting urine cytology in 2013.[8–13] In the recent years, new classification systems with clear criteria have emerged from various institutions from where many institutional well-conducted studies were per-formed; the results of those studies were, however, difficult to compare due to several factors.[6,7]

The emergence of the newly proposed Paris System for Reporting Urine Cytology is regarded as a major step toward standardization in both the cytology and urology fields.[11] At the 2013 International Congress of Cytology, The Paris System (TPS) working group proposed a template with stringent morphologic criteria urging cytopathologists worldwide to categorise urine specimens into one of the following categories: non-diagnostic, negative for HGUC (including reactive/inflammatory changes), atypical urothelial cells (AUC), suspicious for HGUC, HGUC, low-grade urothelial neoplasm (LGUN) and others (including non-malignant entities).[6–8]

In our study, the urine cytology reporting practice at our institute has traditionally followed four categories, i.e unsatisfactory, negative, atypical and positive for malignancy. A large proportion of cases were earlier called “atypical” (41.2%) which included reactive/inflammation/instrumentation induced atypia on one end of the spectrum to severely atypical cells shed in small numbers on the other end Raab et al. observed cytohistological discrepancies in 40.9% of cases. In 63.5% of patients, the discrepancy was attributed to sampling issue, whereas 35.1% was due to an error in interpretation.[14]

After re- assessing the same samples according to TPS criteria, a significant proportion of previous “atypical” categories were upgraded to definite HGUC and SHGUC in our study. There was a high statistical correlation observed when compared the suspicious of carcinoma cases between the Institutional Cytology Report and TPS report.

A cytological diagnosis of high-grade urothelial carcinoma (HGUC) mandates more aggressive follow-up, cystoscopy and biopsy.

In our study, there was a high statistical correlation observed when compared the suspicious of carcinoma cases between the institutional cytology report and biopsy report institute reports. Although cytology scores high in specificity (approximately 90%) in diagnosing HGUC, it is plagued by the low sensitivity of around 55% when all grades are considered together.[2]

This was a retrospective study where the pathologists were aware that biopsies and definitive diagnosis were available, although blinded to the actual diagnosis. Hence, we acknowledge that bias and boldness in re-assigning higher TPS category could have occurred owing to the retrospective nature of the study and the knowledge that it would hardly alter the course of clinical management already initiated. By applying TPS, number of cases assigned to AUC category are very few (7 cases out of 74 with 9.45%).

In our study, there was a high statistical correlation observed when compared the suspicious of carcinoma cases between the biopsy report institute and TPS cytology report reports.

In conclusion, TPS attempts to minimize the subjective bias in urine cytology reporting and do away with the various ambiguous terminologies used worldwide.

5. Conclusion

The TPS seems to improve the performance of urine cytology by limiting the AUC category to cases that are more strongly associated with HGUC.

6. Funding

None

7. Conflict of interest

The authors declare no conflicts of interest

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Table 7: Chi-Square Tests [BiopsyReport Institute and TPS Cytology Report]

Name	PAPILLOMA	PUNLMP	LGUP	HGUC	TOTAL
Negative	2	0	0	0	2
Atypical/ Suspicious	0	2	2	12	16
LGP	3	6	9	3	21
HGUC	0	0	8	27	35
Total	5	8	19	42	74

Table 8: The Paris System basis of urine cytology of total 74 specimens to categorize their carcinoma.

TPS basis					
ND (non diagnostic)	0	0	0	0	0
NHGUC	4	0	2	0	6
AUC	1	4	2	0	7
SHGUC	0	1	1	16	18
HGUC	0	0	0	26	26
LGUN	0	3	14	0	17
Others	0	0	0	0	0
Total	5	8	19	42	74

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Cite this article: Vallamreddy SKR, Begam K V, Pratima J. Implementation of the Paris system versus institutional diagnosis in the performance of urinary cytology: A 5 years correlative study of 74 cases. *Arch Cytol Histopathol Res* 2019;4(3):193-198.