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Papanicolaou Society of Cytopathology System vs World Health Organization of Reporting System for Pancreaticobiliary Cytopathology-Comparison of Risk of Malignancy and Diagnostic Predictive Values: A 3 Year Retrospective Study.

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ABSTRACT

Pancreatic carcinoma is a rare entity with a poor survival rate due to late presentation and limited diagnostic modalities. This retrospective study aimed to evaluate the diagnostic performance of the Papanicolaou Society of Cytopathology (PSC) system and the World Health Organization (WHO) system for pancreaticobiliary cytology reporting. A total of 77 cases with pancreatic lesions were evaluated at the Department of Pathology, Vydehi Institute of Medical Sciences and Research Centre for a period of 3 years, i.e. January 2021 to December 2023, using both PSC and WHO systems. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and diagnostic accuracy were calculated for both systems. The Risk of Malignancy (ROM) was also estimated for each diagnostic category. Both systems showed high sensitivity, specificity and diagnostic accuracy. However, the WHO system had higher sensitivity (95.65% vs 93.47%), NPV (93.75% vs 90.90%) and diagnostic accuracy (96.10% vs 94.81%) compared to the PSC system. The ROM was also accurately estimated by both systems, with the WHO system showing a slightly better performance in stratifying the risk of malignancy. Both PSC and WHO systems are reliable for pancreaticobiliary cytology reporting. However, the WHO system may be a more effective tool for risk stratification and diagnosis of pancreaticobiliary lesions, with a slightly better performance in estimating the ROM. Future studies with larger sample sizes and longer follow-up periods are needed to further validate these findings.

INTRODUCTION

Pancreatic carcinoma is a rare entity being ranked 4th in incidence and 7th in mortality in the world. The incidence rates are highest among the European countries in males and females and the lowest incidence rates were observed in Southeast Asian countries. Pancreatic cancers have become the fourth leading cause of death among all cancers[1]. This poor survival rate is due to late presentation, nonspecific signs and symptoms and also due to limited diagnostic and therapeutic modalities thus causing a need for accurate and timely diagnosis of pancreatic lesions[1]. Imaging modalities play an important role in the diagnosis of pancreatic lesions. Endoscopic ultrasound (EUS) is one of the most sensitive and accurate modalities for the detection and evaluation of pancreatic mass and staging of pancreatic cancer. It gives high-resolution images of the entire pancreas and has been shown to be superior to computed tomography[2]. Another diagnostic modality is cytology. Cytology has proven to be a minimally invasive, rapid and a cost-effective modality for accurately diagnosing pancreaticobiliary lesions and also in some patients it is the only modality to diagnose lesions in this anatomical region. Pancreaticobiliary cytology includes multiple techniques and specimens ranging from brushing, endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) and endoscopic ultrasound-guided fine-needle biopsy (EUS-FNB), among others. EUS-FNA shows high sensitivity and specificity in diagnosing pancreatic lesions, especially solid lesions of the pancreaticobiliary tree[3]. The new edition on standard practice in Cytopathology from the Papanicolaou society of cytopathology (PSC) focuses on the pancreaticobiliary system. The PSC guidelines for pancreaticobiliary cytology include indications, techniques, terminology and nomenclature, ancillary studies and post-procedure management. The World Health Organization (WHO) on the other has recently introduced a new classification system for pancreaticobiliary cytopathology[4]. According to this new classification, PanNET and SPN (Solid pseudo papillary neoplasms) are now categorized as "malignant," while Serous Cystadenoma and lymphangioma have been reclassified as "benign/ negative for malignancy". The previous "neoplastic: other" category has been replaced with two new classifications: "Pancreatic neoplasm-low risk/grade (PaN-Low)" and "pancreatic neoplasm-high risk/grade" (PaN-High). Intra ductal papillary mucinous neoplasm (IPMN) or Mucinous cytic neoplasms (MCN) exhibiting low-to-intermediate-grade dysplasia fall under the PaN-Low category, whereas those with high-grade displace are classified as PaN-High[5]. In this current study, we have studied the cytomorphological features of a set of image guided pancreatic cytologic specimens and then have applied the new proposed terminology for pancreaticobiliary cytology according to both PSC and WHO systems. Our study also compared the outcomes of both the systems for reporting pancreaticobiliary cytopathology and has focused on their respective approaches to risk stratification[6].

Aims of the Study:

- To independently classify categories as defined by the PSC and WHO systems
- To compare the risk of malignancy (ROM) in both classification schemes using archived cytology, histopathology and/or clinical follow-up data.
- To compare sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy of both the systems.

MATERIALS AND METHODS

A three-year retrospective descriptive study was conducted in our tertiary care hospital in India. The investigation included 77 cases., each evaluated using both the PSC system for pancreaticobiliary cytology reporting and the recently introduced WHO reporting system for pancreaticobiliary cytopathology. Patient characteristics such as age, gender, clinical history and family history of pancreatic cancer were recorded. Imaging reports including EUS, US, CT and magnetic resonance cholangiopancreatography were reviewed to assess the location, size and characteristics of the pancreatic lesions. Image guided fixed and unfixed slides were received from the respective pancreatic lesion and they were stained with Papanicolaou, Giemsa, Haematoxylon and Eosin respectively, using standard technique. FNA specimens of other abdominal lesions including peripancreatic lesions, lymph nodes, or bile duct mass lesions were excluded from the study. Onsite evaluation by cytologist was not available in all of these cases. At least one of the experienced cytopathologists involved in our research evaluated the smears. In cases where the diagnosis was uncertain, two or more pathologists reached a consensus. Throughout the entire study duration, the PSC system was consistently employed to categorize pancreaticobiliary cytopathology findings, thus aiding in better communication between different medical specialities. As a result, the PSC categories were assigned prospectively, while the reclassification of cytological outcomes according to the WHO system was done retrospectively in 2024[5]. To ascertain the absolute ROM, each cytological finding was contrasted with either histological or clinical data collected during follow-up. Within each of the groups assigned, it was expressed as the absolute percentage of instances that ultimately received a malignant diagnosis. Histological samples from other modalities (repeated biopsy, surgical specimen, autopsy) or without them, the radiologic and clinical evidence of neoplasm (radiologic progression of disease, metastasis formation) were further used to support a malignant diagnosis[7].

Primary and metastatic carcinomas, NETs (Neuroendocrine tumors), neuroendocrine carcinomas, (SPN), sarcomas and hematolymphoid malignancies were among the malignant histologic follow-up findings included in the calculation of ROM. A benign lesion was defined as one that did not show any clinical, radiologic, or other signs of disease development over the course of the follow-up[7]. As this was a retrospective study, no separate informed consent was deemed necessary and the study was approved by the Institutional Ethics Committee.

RESULTS AND DISCUSSIONS

The present study was undertaken from a set of archived data from January 2021 to December 2023 at the Department of Pathology, Vydehi Institute of Medical Sciences and Research Centre in Bangalore, Karnataka that included a total 77 cases with a lesion in the pancreas. The average range of patient's ages 41–50 years (21 cases) with a median age of patients being 49years. The cases among men were 57.1% (44 cases) and women were 42.8% (33 cases). There was a female preponderance with a ratio of male to female being 1.33:1 (Fig. 1).

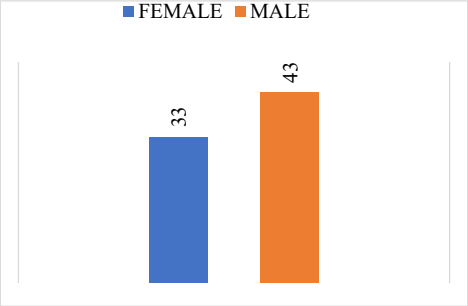

Fig. 1: Gender Distribution

Abdominal pain (82%), weight loss (31%) and jaundice (17%) were the most common symptoms and Malena was the least common symptom (8%). Location of the lesions, the head of the pancreas being most common (77%) followed by tail (10 %), body (9 %) and finally the neck (4%) (Fig. 2).

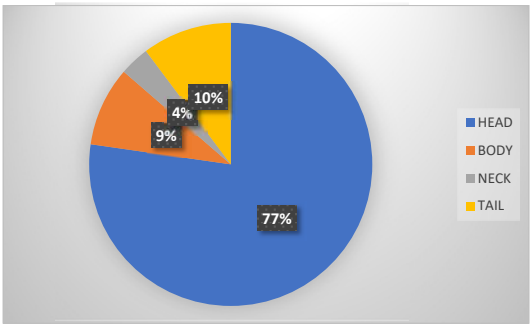

Fig. 2: Site of Pancreatic Lesions

EUS guided-FNAC was the most common (72.7%) modality of imaging followed by USG guided-FNAC (24.6%) and finally ERCP guided-FNAC (2.5%) (Fig. 3).

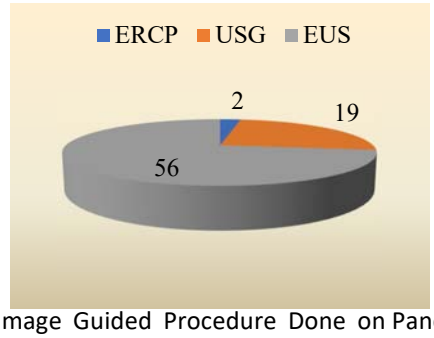

Fig. 3: Image Guided Procedure Done on Pancreatic Lesions

The pancreatic lesions were already categorized according to the PSC system prospectively, while the reclassification of cytological outcomes according to the WHO system was done retrospectively (Fig. 4). The benign lesions which was most commonly seen was chronic pancreatitis and the most common lesion under positive for malignancy was adenocarcinoma (Table 1).

Table 1: Number and Percentage of Cases Categorized According to PSC System for Reporting Pancreaticobiliary Cytopathology and Who Reporting System for Pancreaticobiliary Cytopathology

PSC	Number (%)	WHO	Number (%)
I. Non-Diagnostic	14 (18.18%)	I. Non-Diagnostic	14 (18.18%)
II. Negative for Malignancy	16 (20.78%)	II. Negative for Malignancy	16 (20.78%)
III. Atypical	1 (1.29%)	III. Atypical	1 (1.29%)
IV. Neoplastic Lesions		IV. Pancreatic Neoplasms-Low Grade	1 (1.29%)
A. Benign	0		
B. Others	2 (2.59%)		
V. Suspicious for Malignancy	6 (7.79%)	V. Pancreatic Neoplasms-High Grade	0
VI. Positive for Malignancy	38 (49.35%)	VI. Suspicious for Malignancy	6 (7.79%)
		VII. Positive for Malignancy	39 (50.64%)

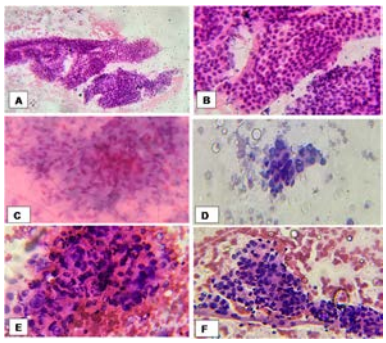

Fig. 4: Cytopathology of Most Common Pancreatic Lesions seen in the Current Study and Categorization of the Lesions Under WHO and PSC System for Reporting Pancreaticobiliary Cytopathology:
(A) and (B) Benign Pancreatic Tissue-Negative for Malignancy (PSC II and WHO II, HandE 10X and 40X)
(C) Granulomatous Inflammation-Negative for Malignancy (PSC II and WHO II, Pap Stain 40X)
(D) Suspicious for Malignancy (PSC V and WHO VI, HandE 40X)
(E) Poorly Differentiated Carcinoma (PSC VI and WHO VII, HandE 40X)
(F) Positive for Malignancy-Possibly Adenocarcinoma (PSC VI and WHO VII, HandE 10X)

Follow-up histological reports were available for 19 numbers of cases (Fig. 5). Radiological and clinical follow-up data were used for all cases. The histologic specimens included small biopsy samples obtained using modalities, like trans abdominal core needle biopsies and endoscopic biopsies from tumors and surgical excision or resection of pancreatic specimens.

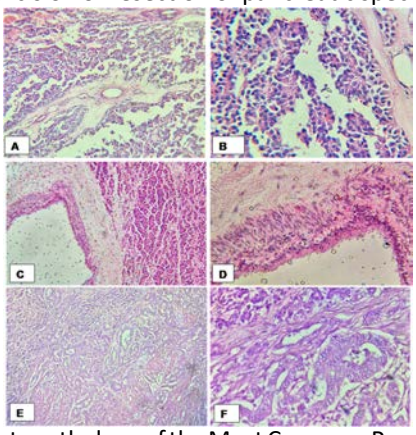

Fig. 5: Histopathology of the Most Common Pancreatic Lesions Seen in the Current Study: (HandE, 10X and 40X)
(A and B) Solid Pseudo Papillary Neoplasm
(C and D) Mucinous Cystic Neoplasm, (E and F) Well Differentiated Adenocarcinoma

To evaluate the risk of malignancy (ROM), histologic correlation was utilized. If histology was found unavailable, cytologic diagnoses of malignancy were classified as true positives if clinical follow-up revealed clear malignant characteristics or metastasis. Benign cytologic results considered true negatives if histology confirmed a benign neoplasm, or, in the absence of histology, if clinical follow-up showed no evidence of malignancy or metastasis. ROM for each diagnostic category was calculated by dividing the number of malignant cases (determined through cytology, histopathology, or clinical follow-up) by the total number of malignancy cases in that category. Corresponding to these, the absolute ROM of the "non-diagnostic" (PSC I and WHO I) category were 4.5% and 4.4% respectively, "negative for malignancy" (PSC II and WHO II) category and "atypical" (PSC III and WHO III) category were 0%. The clinical and endosonographic picture was most useful in deriving ROM in these categories. Despite the heterogeneous nature of the "neoplastic: other" (PSC IVb) category of the PSC system, the absolute ROM was 2.2%. This category included 2 well-differentiated NETs on cytology out of which one of the cases was diagnostically overestimated on cytology having the impression of Chronic pancreatitis (false positive) in histopathological examination and whereas the other case was confirmed on histopathology as malignancy, categorised correctly as Malignant(WHO VII) according to WHO. All the cases in the "Suspicious for Malignancy" (PSC V and WHO VI) category also had a definitive diagnosis of malignancy. In the "Malignant" (PSC VI and WHO VII) category , the absolute ROMs were 100 % in PSC and 97.7% in WHO due to the same well differentiated NET as described above which had a diagnosis of chronic pancreatitis on histopathological examination (Table 2).

Table 2: Risk of Malignancy According to PSC System for Reporting Pancreaticobiliary Cytopathology and Who Reporting System for Pancreaticobiliary Cytopathology

PSC	Rom	Who	Rom	P-value
I. Non-Diagnostic	4.5%	I. Non-Diagnostic	4.4%	**<0.05**
II. Negative for Malignancy	0%	II. Neagtive for Malignancy	0%	
III. Atypical	0%	III Atypical	0%	
IV. Neoplastic Benign Others	2.2%	IV. Pancreatic Neoplasms-Low Grade	0%	
V. Suspicious for Malignancy	100%	V. Pancreatic Neoplasms-High Grade	0%	
VI. Positive for Malignancy	100%	VI. Suspicious for Malignancy	100%	
		VII. Positive for Malignancy	97.7%	

In all of these cases of malignancy, the malignant nature of these tumors is supported by clinical and radiological progressive disease course, aided by histopathological verification. Though histopathological examination was done in very few cases (19 cases) due to patients' refusal of curative surgery in the rest of the cases. P values were assessed using Chi square/Fisher exact test. Statistical significance was established at P =<0.05. Both the systems has a P value of less than 0.05, since both systems have highly significant p-values they both perform well in distinguishing between different categories. Whereas, Sensitivity, Specificity, Positive Predictive Value, Negative Predictive Value and diagnostic accuracy of the cytopathological evaluation using both PSC (93.47%, 96.77%, 97.72%, 90.90% and 94.81%) and WHO (95.65%, 96.77%, 97.78%, 93.75%, 96.10%) systems were calculated (Table 3). Though, both systems have similar specificity and NPV. Overall, the WHO system appears to be slightly better than the PSC system due to its higher sensitivity, NPV and diagnostic accuracy.

Table 3: Diagnostic Predictive Values According to PSC System for Reporting Pancreaticobiliary Cytopathology and WHO Reporting System for Pancreaticobiliary Cytopathology

PSC		Who	
Sensitivity	93.47%	Sensitivity	95.6%
Specicificity	96.77%	Specicificity	96.77%
Positive Predictive Value	97.72%	Positive Predictive Value	97.78%
Negative Predictive Value	90.90%	Negative Predictive Value	93.75%
Diagnostic Accuracy	94.81%	Diagnostic Accuracy	96.10%

The diagnosis of solid pancreatic lesions has undergone significant advancements in recent years, with Endoscopic Ultrasonography-guided Fine-Needle Aspiration (EUS-FNA) emerging as a primary diagnostic modality. To standardize the reporting of EUS-FNA cytology results, the Papanicolaou Society of Cytopathology (PSC) system was developed. However, limitations in the PSC system led to the introduction of a new World Health Organization (WHO) classification

system in 2022. While this new system aims to improve diagnostic accuracy and risk stratification, further research is needed to fully validate its effectiveness in clinical practice. This study assessed the diagnostic performance of the Papanicolaou Society of Cytopathology (PSC) system and the World Health Organization (WHO) system for pancreaticobiliary cytology reporting, with a focus on sensitivity, specificity and diagnostic accuracy. The results revealed that both systems performed reliably, but the WHO system demonstrated a slight edge in terms of diagnostic predictive values particularly with regards to the reclassification of the PSC IVb category[8]. Numerous prospective and retrospective studies have evaluated the Risk of Malignancy (ROM) values associated with the standardized categories of the Papanicolaou Society of Cytopathology (PSC) system. These studies have revealed significant variability in ROM values across most categories. However, two exceptions are notable: the PSC V (suspicious for malignancy) and PSC VI (malignant) categories, which have consistently demonstrated high ROM values."Study by Layfield and team (2014) reported ROM values of 21.4% for Category I, 12.6% for Category II and 73.9% for Category III (7). Chen group (2017) documented higher ROM values for Categories I (57.1%), II (18.1%) and III (69.2%)[8]. Conversely, Hoda *et al.* (2019) reported lower ROM values for these categories, with 7.7%, 1% and 28%, respectively[9]. Similar to our findings, Hoda group (2019) and Vasas group (2024) reported low ROM values for Category II (0-2.2%) (9,4). Additionally, high ROM values for Category V (94.7–100%) have been consistently reported by Kundu (2023) and Vasas (2024) group, aligning with our study's findings of a 100% ROM for this category[2,4]. The ROM values for the WHO system also varied across studies. Hoda group (2022) reported values of 7.7% for Category I, 1% for Category II and 28% for Category III[10]. In contrast, Gocun group (2022) observed higher ROM values for Category I (35%) and Category III (69%)[6], while Kundu *et al.* (2023) reported ROM values of 60% for Category I, 21.3% for Category II and 35.7% for Category III (4). High ROM values for Categories VI (91-100%) and VII (94.9-100%) were consistently observed in studies by Hoda *et al.* (2022), Gocun *et al.* (2022) and Kundu *et al.* (2023), similar to the current study. These findings emphasize the robustness of the WHO system in predicting malignancy in higher categories. The diagnostic predictive values in this study for the PSC system were comparable to those reported by Ilyas *et al.* (2022), with similar sensitivity (93.47% vs. 92.8%) and specificity (96.77% vs. 100%). However, the negative predictive value (NPV) in our study (90.9%) was slightly lower than that of Ilyas *et al.* (2022) (92.5%). Wright *et al.* (2018) reported higher sensitivity (95.4%) and specificity (100%)[11], whereas Gonzalez *et al.* (2021) documented lower specificity (88.4%) and NPV (84.4%)[12]. For the WHO system, this study observed slightly higher diagnostic predictive values compared to Lui *et al.* (2023), particularly in sensitivity (95.65% vs. 90.3%) and NPV (93.75% vs. 70.4%)[13]. Notably, Vasas et al. (2024) reported even higher sensitivity (99.72%) and specificity (95.56%) for the WHO system. These findings suggest the WHO system may provide greater diagnostic reliability and predictive accuracy.

CONCLUSION

This retrospective analysis highlights the strong diagnostic performance of both the PSC and WHO systems for pancreaticobiliary cytology reporting. Both systems demonstrated high sensitivity, specificity and diagnostic accuracy. However, the WHO system outperformed the PSC system slightly, with better sensitivity, NPV and overall diagnostic accuracy. These results support the use of both systems in clinical practice, while suggesting that the WHO system may be more effective for risk stratification and diagnosis of pancreaticobiliary lesions. Further studies with larger cohorts and extended follow-up are warranted to validate these findings and refine the utility of these systems in clinical practice.

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