Original Article

Diagnostic Efficacy of Brush Cytology in the Evaluation of Extrahepatic Bile Duct Strictures: Experience from a Tertiary Care Centre in Northern India

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Abstract

Background: Endoscopic evaluation is critical in assessing the cause of obstructive jaundice. Biliary brushings during endoscopic retrograde cholangiopancreatography (ERCP) or percutaneous transhepatic cholangiography (PTC) are widely used for obtaining a tissue sample. This study was undertaken to investigate the role of endoscopic biliary tract brush cytology as a diagnostic tool in extrahepatic biliary strictures.

Materials and Methods: During the 6-year study period, 80 jaundiced patients underwent ERCP (n=63) / PTC (n=17) along with cytological evaluation of biliary brushings. Demographic data and relevant clinico-radiological details were retrospectively retrieved from institutional records. The corresponding cytological smears were re-evaluated and classified as: (i) unsatisfactory/inadequate; (ii) negative (including benign and reactive); (iii) suspicious for malignancy; (iv) positive for malignancy. Cytology results were compared with final diagnosis (defined as either definitive tissue diagnosis or clinico-radiological follow-up), and sensitivity (SN), specificity (SP), positive predictive value (PPV), negative predictive value (NPV), and diagnostic accuracy (DA) were calculated.

Results: The age group of patients ranged from 15 to 85 years, with mean age of presentation being 52.7 years. Cytologic diagnosis was: positive for malignancy in 23 (26.7%), suspicious in 8 (9.3%), and benign/reactive/negative in 52 (60.5%) cases. In the 61 cases where the final diagnosis was available, the overall SN, SP, PPV, NPV, and DA of biliary brush cytology were 68.57%, 92.31%, 92.31%, 68.57%, and 78.69%, respectively. There was no significant difference in DA of brushings obtained at ERCP compared to those from PTC.

Conclusion: We found directly-smeared brush cytology to be diagnostically reliable, moderately sensitive, and highly specific for diagnosing common bile duct lesions encountered at ERCP/PTC.

Keywords:

Brush cytology, Common bile duct, Endoscopic retrograde cholangiopancreatography, Obstructive jaundice, Percutaneous transhepatic cholangiography

Introduction

Common bile duct (CBD) strictures are caused by inflammatory or neoplastic processes involving the gallbladder, biliary tree, ampulla, or pancreas. These lesions are not always readily accessible to biopsy, and hence brush cytology performed at endoscopic

retrograde cholangiopancreatography (ERCP) or percutaneous transhepatic cholangiography (PTC) has become the preferred initial modality for attaining tissue diagnosis in patients with extra-hepatic biliary strictures. However, various workers have reported variable sensitivity and specificity of this modality [1–3]. Also, there is a glaring paucity of Indian literature in this context. Hence, we performed a retrospective analytical study to determine the diagnostic accuracy, sensitivity, and specificity of brushings obtained at ERCP and PTC in evaluating extra-hepatic biliary strictures of different etiologies in the Indian setup.

Materials and Methods

All patients who underwent ERCP or PTC procedures along with endobiliary brushing, between January 2012 and December 2017, were retrospectively identified from the institutional electronic database. Patients' age, gender, presenting symptoms, physical examination and radiological findings, anatomical location of the CBD stricture, corresponding biopsy or fine needle aspiration cytology (FNAC) results, the definitive diagnosis, and follow-up details were obtained from the hospital information system and medical records. The cytology slides were retrieved from the departmental archives. The brushings were obtained at ERCP or PTC by passing the brush over a guide wire placed across the stricture under fluoroscopic guidance. The procured material was smeared from the brush onto two to six glass slides immediately on-site. One to two smears were wet-fixed in 95% ethanol; the rest were air-dried and transported to the cytopathology laboratory for further processing. The May-Grünwald-Giemsa-stained and Hematoxylin-Eosin-stained slides were reviewed independently by two pathologists for adequacy and cytomorphological details (hypercellularity, presence of 2-cell population, cellular discohesion, 3-dimensional architecture, nuclear contour irregularity, nuclear pleomorphism, nuclear hypo- or hyperchromasia, high nuclear-cytoplasmic ratio, nuclear moulding, cytoplasmic mucin, presence of prominent nucleoli, mitosis, necrosis, inflammatory cells, presence/absence of bile) [4], and a common consensus was reached in each case. If the archival slides were faded, then re-staining was done before the final cytomorphologic evaluation.

The brush smears were categorised cytologically as: Category I: Inadequate/unsatisfactory, Category II: Negative for malignancy/benign/reactive, Category III: Suspicious for malignancy, Category IV: Positive for malignancy

This four-tiered classification was devised by the authors for the current study, drawing from criteria used in prior biliary cytology studies. A sample was considered inadequate if it had fewer than five clusters with ≤10 well-preserved cells per cluster [1]. Representative microphotographs are shown in Figure 1.

The final diagnosis (benign or malignant), achieved either by microscopic confirmation (endoscopic ultrasound-guided fine needle aspiration, endoscopic biopsy, or surgical resection) or by clinical course (clinical or imaging features of malignancy during a minimum follow-up of six months), was available in 61 patients. In the remaining 19 patients, the nature of the stricture remained undetermined; therefore, these patients were excluded from further analysis. For the purpose of statistical analysis, category I and II cases were considered as 'negative,' while category III and IV samples were deemed as the 'positive' group. Sensitivity, specificity, positive and negative predictive value, and diagnostic accuracy were determined. A brief outline of the study methodology is depicted in Figure 2.

Results

During the 6-year study period, 80 jaundiced patients underwent ERCP/PTC along with brush cytology. Of these, four patients had two cytological samples and one patient had three cytological samples, yielding a total of 86 specimens. Each specimen was analyzed as an independent diagnostic attempt, in keeping with our objective to assess the real-world diagnostic yield of individual

brush passes. Forty-five patients (56.25%) were men and 35 (43.75%) were women, with a mean age of 52.7 years (range 15 to 85 years). The frequency of stricture location was as follows: proximal bile duct 21.25% (n=17), mid bile duct 18.75% (n=15), and distal bile duct 50.0% (n=40). Eight patients (10.0%) had multiple or long-segment strictures.

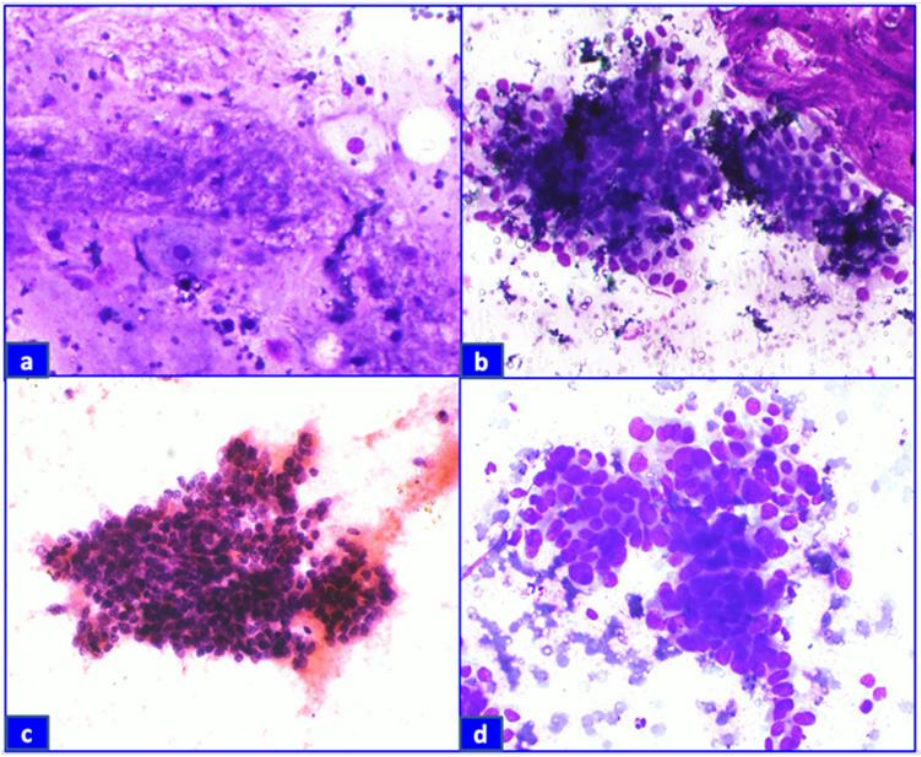

Figure 1:a: Category I (Unsatisfactory/ Inadequate)-Microphotograph showing inadequate cytosmears comprising of few macrophages with no epithelial cell component [May Grunwald Giemsa stain, 200x magnification]; b:Category II (Negative/ Benign/ Reactive)– A monolayered sheet of benign ductal cells with superimposed specks of bile (black) [May Grunwald Giemsa stain, 200x magnification]; b:Category III (Suspicious For Malignancy)- Sheet of ductal cells displaying nuclear crowding and overlapping, nuclear hyperchromasia and coarse chromatin [Papinocolaou stain, 200x magnification]; d:Category IV(Positive For Malignancy)- Tumor cells displaying nucleomegaly, anisonucleosis, hyperchromasia, nuclear molding, nuclear membrane irregularity and clumped chromatin. [May Grunwald Giemsa stain, 200x magnification]

On cytological evaluation, the majority of the biliary brushings (n=52, 60.5%) were benign/negative/reactive, 23 (26.7%) samples were positive for malignancy, 8 (9.3%) had suspicious cytology, and 3 (3.5%) were inadequate/unsatisfactory [Table 1].

A confirmatory tissue diagnosis was available in 36 cases (45%). The tumors (n=24) encountered were cholangiocarcinoma (n=11), periampullary adenocarcinoma (n=6), gallbladder adenocarcinoma (n=5), and pancreatic adenocarcinoma (n=2). Benign lesions (n=12) included 5 cases of inflammatory stricture, 4 cases of postoperative stricture, 2 cases of chronic pancreatitis, and a single case of primary sclerosing cholangitis (PSC). Based on follow-up and clinico-radiological features, 11 cases were considered malignant, and 14 cases had a benign course. Nineteen patients (23.75%) were eventually excluded from further analyses (14 negative/benign, 2 suspicious, 3 positive for malignancy on cytology) due to lack of histologic/radiologic confirmation of disease or clinical follow-up.

The sensitivity, specificity, positive predictive and negative predictive values, as well as the diagnostic accuracy, are presented in [Table 2].

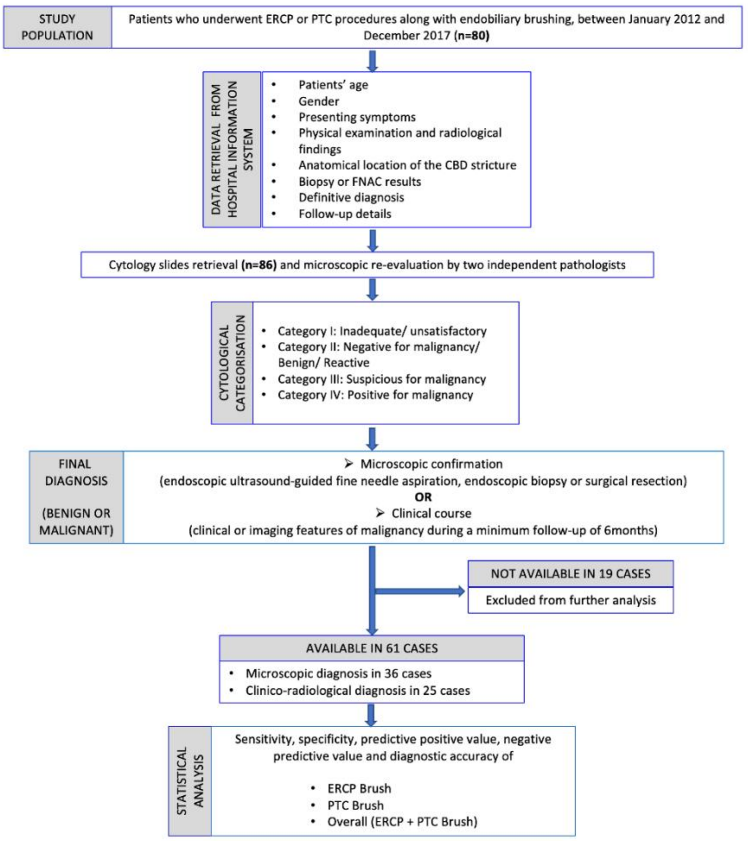

Figure 2: Flowchart briefly depicting the study methodology

Table 1: Cytological Categorization of Endobiliary Brush Smears Obtained During Endoscopic Retrograde Cholangiopancreatography (ERCP) and Percutaneous Transhepatic Cholangiography (PTC)

Method	Total Number of Patients	Total Number of Samples	Category I: Unsatisfactory/Inadequate	Category II: Negative/Benign/Reactive	Category III: Suspicious	Category IV: Malignant
ERCP Brush	63	69*	2	45	6	16
PTC Brush	17	17	1	7	2	7
Total	80	86	3	52	8	23
Five patients had more than one cytological sample.						

Table 2: Sensitivity (SN), Specificity (SP), Positive Predictive Value (PPV), Negative Predictive Value (NPV), and Diagnostic Accuracy (DA) of Endobiliary Brush Smears Obtained During Endoscopic Retrograde Cholangiopancreatography (ERCP) and Percutaneous Transhepatic Cholangiography (PTC)

Method	SN % (95% CI)	SP % (95% CI)	PPV % (95% CI)	NPV % (95% CI)	DA % (95% CI)
ERCP Brush	66.7 (44.7–84.4)	95.7 (78.0–99.9)	94.1 (69.7–99.1)	73.3 (60.8–83.0)	80.9 (66.7–90.9)
PTC Brush	72.7 (39.0–94.0)	66.7 (9.4–99.2)	88.9 (60.8–97.6)	40.0 (16.0–70.0)	71.4 (41.9–91.6)
Overall (ERCP+PTC)	68.6 (50.7–83.2)	92.3 (74.9–99.1)	92.3 (75.7–97.9)	68.6 (56.9–78.3)	78.7 (66.3–88.1)
The values within the parentheses denote 95% confidence intervals.					

Discussion

The endobiliary brushings obtained under ERCP/PTC guidance produced adequately cellular smears with well-preserved cellular morphology in most instances. Only three specimens (3.5%) were considered inadequate for diagnosis in our study cohort, which is in par with the inadequacy rates reported in other similar studies [3, 5–8]. All three patients had distal CBD stricture. Later on, two of them were diagnosed with cholangiocarcinoma on resected specimen. There were eleven false-negative results in our series (nine reported as 'negative for malignant cells' and two as 'inadequate/unsatisfactory'). Logrono and colleagues cited that sampling errors, interpretive errors, and technical errors accounted for 66%, 17%, and 17% false-negative cytodiagnoses, respectively, in their series [9]. As a policy of our lab, routine reporting/interpretation is made at a multi-headed microscope after reaching a consensus, thereby eliminating any interobserver disagreement. This is also reflected by the fact that, during review, none of the previous diagnoses was changed. False-negative cytology may also be due to submucosal location of the lesion, strictures secondary to external compression of the biliary tract, difficult anatomical location of the lesion, and extensive fibrosis.

Suspicious cytology comprised 9.3% (n=8) of our cases, amongst which two were false positive. One case showed marked reactive atypia in the distal CBD in the setting of acute-on-chronic calcific pancreatitis (Whipple's resection), and the other displayed features of reactive atypia secondary to cholangitis (intraductal forceps biopsy). Glasbrenner and colleagues also had similar experiences, wherein chronic pancreatitis and other inflammatory pathology led to false-positive diagnoses [10]. This emphasizes the fact that, at times, inflammation can induce alarming cytological changes, and the pathologist as well as the treating surgeon should be aware of this well-known pitfall in bile duct cytology. In such scenarios, an intraductal forceps biopsy or repeat brushing should be considered prior to a definitive surgical procedure. Few investigators have attempted to further categorize the suspicious dysplastic cells on cytology into low-grade and high-grade dysplasia [11–13]. This was not done in our study, as we feel such dichotomization has low reproducibility among pathologists and also has meager impact on the management course.

We found modest overall sensitivity (68.576%), high specificity (92.31%), high positive predictive value (92.31%), and moderate diagnostic accuracy (78.69%), a result in concordance with the existing literature as depicted under Table-3 [1–3, 7, 10, 14–20]. Burnett et al. reviewed 16 studies, combined their data, and obtained a pooled sensitivity of 41.6% for endobiliary brush cytology [21]. In another systematic review by Navaneethan U et al., cumulative sensitivity and specificity of endobiliary brushings in detecting malignant biliary strictures were 45% and 99%, respectively [22]. de Peralta-Venturina et al. and Soyuer et al. found ERCP-guided brush cytology to be more sensitive and specific than smears prepared at PTC [3, 20]. In our study cohort, ERCP brushing performed better than PTC brushings at distinguishing between the 'positive' and 'negative' groups (AUC 0.98 vs. AUC 0.90; Figure 3). However, although the specificity and diagnostic accuracy of ERCP were higher than PTC, the brushings obtained at PTC performed better than those of ERCP in terms of sensitivity [Table-2]. Many investigators have studied the sensitivity and specificity of biliary cytology in patients with primary sclerosing cholangitis, with sensitivity ranging from 36%–83% and specificity ranging from 95%–100% [11, 19, 23, 24]. We encountered only a single case of primary sclerosing cholangitis, which had negative cytology.

We received repeated endobiliary brushings in five patients, amongst whom four patients had two samples each, while one patient had three brushings [Table-4]. In two patients, the initial cytology was suspicious for malignancy and the repeat smears were negative, but only one of them had malignancy. One patient, who had three cytologically negative brush smears, was later diagnosed with cholangiocarcinoma on intraductal forceps biopsy. Hence, in our experience, repeat smears did not add to the

diagnostic value, in contrast to other authors' views advocating repeated brushings to increase the cancer detection rate [7, 25, 26]. However, the number of patients undergoing repeat sampling is too small in our study cohort to draw definite conclusions.

Table 3: Comparison of Sensitivity (SN), Specificity (SP), Positive Predictive Value (PPV), Negative Predictive Value (NPV), and Diagnostic Accuracy (DA) of Endobiliary Brush Cytology Across Various Studies

Authors	SN %	SP %	PPV %	NPV %	DA %
Present Study	68.6	92.3	92.3	68.6	78.7
Peralta-Venturina et al[3]	88.9	95.7	96	88	92
Ding et al[14]	79.4	85.7	-	-	-
Govil et al[15]	68	100	-	-	-
Mehmood et al[16]	65.3	100	100	27	-
Temiño et al[17]	62	100	100	58	-
Mahmoudi et al[18]	61	98	99	57	-
Stewart et al[7]	59.8	98.1	98	61.3	-
Ferrari et al[2]	56.2	100	100	51.2	70
Glasbrenner et al[10]	56.1	90.5	94.1	43.2	65.4
Lindberg et al[19]	55	100	100	66	76
Soyuer et al[20]	48	100	100	69	75
Costa et al[1]	40	100	100	55	65.4

Table 4: Cytological and Final Diagnosis of Patients With More Than One Endobiliary Brush Sample

	Age/Gender	Initial Cyto-Diagnosis	Diagnosis on Repeat Brushings	Final Diagnosis
Patient 1	30/Male	Suspicious (Category III)	Negative (Category II)	Benign[a,b]
Patient 2	67/Male	Suspicious (Category III)	Negative (Category II)	Malignant[b]
Patient 3	74/Male	Negative (Category II)	Negative (Category II)	Malignant[a]
Patient 4	68/Female	Negative (Category II)	Negative (Category II)	Benign[b]
Patient 5	52/Female	Negative (Category II)	Negative (Category II)	Malignant[a]
a = Histopathological diagnosis; b = Clinico-radiological diagnosis.				

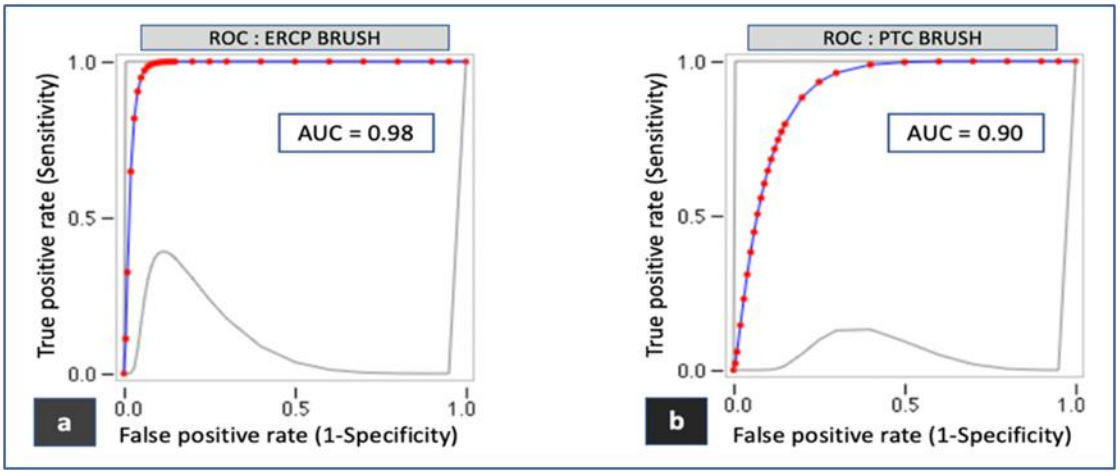

Figure 3: Receiver operating curve (ROC) for endobiliary brushings at ERCP(a) and PTC(b): The blue line with red dots indicates the smoothed ROC. The grey lines denote the 95 % confidence interval of the ROC. Area under ROC curve (AUC) is >0.5 and <1.0 for both

Stricture dilation and manipulation have been shown to improve the yield of biliary brush cytology [25, 27, 28]. In this regard, various investigators have utilized different techniques such as the 10F Howell device/Cook Endoscopy by Farrell et al. [28], scraping brush by Parasher and Huibregtse [29], Soehendra stent retriever by Brand et al. [30], and basket cytology by Bang et al. [31]. Fogel et al. obtained a better cellular yield with a larger and stiffer cytology brush (Cytolong brush), but unfortunately, the increased cellularity did not translate into improved sensitivity, and the investigator also experienced difficulty in stricture negotiation [32]. One of the major drawbacks of our study is that, being retrospective in nature, information regarding whether the sampling was done prior to or after stricture dilation was not available.

The use of liquid-based technologies is gaining popularity for the preparation of non-gynecological specimens, and this holds true for bile duct brushing specimens also. Volmar et al. [8] and Ylagan et al. [33] opined that ThinPrep liquid-based technology is advantageous over direct brush smears, as it eliminates air-drying artifact, lyses RBCs, decreases overlapping of cells, and provides better preservation of 3D micropapillary structures. Volmar et al. [8] also stated that the combination of both direct brush smear and ThinPrep method was superior to either direct smear with cytospin or direct smear alone in terms of improved sensitivity and diagnostic accuracy. Similarly, in a more recent comparative study by Siddiqui et al. [4], ThinPrep smears of bile duct brushings showed better cellularity and cellular preservation and better sensitivity (77% vs. 66%) when compared with conventional smears. Also, cell-block preparation has been shown to increase the diagnostic value of endobiliary brushings [1].

In an effort to further enhance the sensitivity of biliary brushing cytology, various ancillary techniques have been investigated. Mutational analysis of p53 and K-RAS in biliary brushings has been attempted by various authors but has yielded contradictory results [35–39]. In the study by Lindberg B et al. [19], flow cytometric DNA measurements for aneuploidy had lower sensitivity (52% vs. 55%) and specificity (96% vs. 100%) than brush cytology, whereas Ryan and Baldauf [40] improved the sensitivity from 42% (brush cytology only) to 63% by combining cytology with flow cytometric analysis. Levy et al. [41] showed that digital image analysis (DIA), fluorescent in-situ hybridization (FISH), and combined DIA/FISH significantly improved the diagnostic yield of biliary brushings. Kipp and colleagues [42] performed FISH on bile duct aspiration and brushing specimens using a mixture of fluorescently labeled probes to centromeres of chromosomes 3, 7, and 17 and chromosomal band 9p21, and reported the assay to be significantly more sensitive than conventional bile duct cytology. Recently, Keane MG et al. [43] measured the levels of minichromosome maintenance replication protein 5 (MCM5) in biliary brush samples using immunocolorimetric ELISA assay and concluded that MCM5 is a more sensitive indicator of pancreatico-biliary malignancy than standard brush cytology (55.6% vs. 25.0%). However, such advanced diagnostic modalities are not in common use at all hospitals and are available only at a few select centers. Also, additional research with larger sample sizes needs to be carried out to establish the role of these molecular techniques as an adjunct in routine biliary brush specimens.

Conclusion

We found directly-smeared brush cytology to be diagnostically reliable, moderately sensitive, and highly specific for diagnosing common bile duct lesions encountered at ERCP/PTC. Thus, it could be reliably used as a first-line diagnostic modality in the evaluation of extrahepatic biliary strictures. The specificity and diagnostic accuracy of ERCP brushings were higher than PTC brushings, whereas the brushings obtained at PTC performed better than those of ERCP in terms of sensitivity. The study reaffirms that false-negative results can occur due to factors such as submucosal lesions and technical limitations, emphasizing the need for repeat procedures or additional biopsy techniques in suspicious cases. Additionally, while advanced techniques like ThinPrep, cell block preparation, and molecular diagnostics show promise in enhancing diagnostic accuracy, their widespread adoption is

limited by availability and cost considerations. Overall, despite inherent limitations, endobiliary brush cytology remains a valuable diagnostic modality for biliary strictures, with potential improvements through the integration of advanced diagnostic methods in the future.

***Abbreviations**:*

MGG – May-Grunwald Giemsa, PAP – Papanicolaou stain, NHGUC – Negative for High-Grade Urothelial Carcinoma, AUS – Atypical Urothelial Cell, LGUC – Low-grade urothelial neoplasm, HGUC – High-grade urothelial carcinoma, PUNLMP – Papillary urothelial neoplasm of low malignant potential

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