ORIGINAL RESEARCH PAPER

Gastroenterology

KEY WORDS: Benign biliary strictures, cholangioscopy, endoscopic retrograde cholangiopancreatography.

# BRUSH CYTOLOGY IN PANCREATOBILIARY MALIGNANCIES : STILL A USEFUL TOOL

**Dr. Sanjay Kumar*** Consultant & Head Department of Gastroenterology, Gastrocare Liver and Digestive Disease Center, Bhopal *Corresponding Author

**Dr. Neetu Kumar** Consultant and Head Department of Pathology, Gastrocare Liver and Digestive Disease Center, Bhopal

**Dr. Pravin Borsadia** Consultant Gastroenterology, Gastrocare Liver and Digestive Disease Center, Bhopal

**Dr. Sandesh Sharma** Consultant and Head Department of Surgery, Gastrocare Liver and Digestive Disease Center, Bhopal

**Dr. Varun Khandagale** Consultant Gastroenterology, Gastrocare Liver and Digestive Disease Center, Bhopal

**Dr. Kshitij Kumar** Research Fellow Department of Gastroenterology, Gastrocare Liver and Digestive Disease Center, Bhopal

ABSTRACT

**Objectives:** TO assess the diagnostic yield of cytology, cholangioscopy, cholangioscopic biopsy and CA-19.9 in patients with malignant obstructive jaundice

**Methodology:** We conducted a retrospective analysis of consecutive cases of malignant obstructive jaundice/ GB mass/ Pancreatic mass, based on imaging and subjected them to the appropriate cytological examination and CA 19-9 assays and compared them with clinical, radiological and surgical diagnosis.

**Results:** The diagnostic yield was 61.5% (48/78). It was more for Brush smear (70%) as compared to Bile (50%). Spyglass cholangioscopy was suggestive of malignancy in 8/10, out of which spybite was taken in 2, both of which turned out to be positive. But we switched over to brush cytology as we found spy forceps difficult to use. CA 19.9 levels were available in 30 of 48 confirmed cases and were >500 in 20, between 100 & 500 in 2, between 30 & 100 in 6 and normal in 2. But CA 19.9 levels were also raised to >500 in 4/5 cases of CBD stones with cholangitis

**Conclusion:** Brush cytology in our set up is a very good tool and yield is about 70% .Very high levels of ca 19.9 are suggestive but cannot be relied upon as a sole evidence of malignancy. Spyglass images strengthen the diagnosis of cholangiocarcinoma but spybite is not a practical tool as passage through spy scope is very difficult and time consuming

## INTRODUCTION

Biliary strictures frequently present a challenge in terms of diagnosis, which requires a multidisciplinary approach. Biliary strictures present a diagnostic challenge, especially when no etiology can be ascertained after laboratory evaluation, abdominal imaging and endoscopic retrograde cholangiopancreatography (ERCP) sampling. These strictures were traditionally classified as indeterminate strictures, although with advances in endoscopic techniques and better understanding of hepato-biliary pathology, more are being correctly diagnosed. The implications of missing a malignancy in patients with biliary strictures—and hence delaying surgery—are grave but a significant number of patients (up to 20%) undergoing surgery for suspected biliary malignancy can have benign pathology. The diagnostic approach to these patients involves detailed history and physical examination and depends on the presence or absence of jaundice, level of obstruction, and presence or absence of a mass lesion. While abdominal imaging helps to find the level of obstruction and provides a 'road map' for further endoscopic investigations, tissue diagnosis is usually needed to make decisions on management. Initially ERCP was the only modality to investigate these strictures but now, with the development of endoscopic ultrasound with fine needle aspiration and the availability of newer techniques such as intraductal ultrasound, single-operator cholangioscopy and confocal laser endomicroscopy, the diagnostic approach to biliary strictures has changed significantly.

Traditionally, biliary strictures have been considered to be indeterminate when a diagnosis cannot be made after basic laboratory work-up, abdominal imaging and endoscopic retrograde cholangiopancreatography (ERCP) with biliary sampling. Alhough up to 30% of biliary strictures can be benign , the vast majority are malignant, the two major malignancies being pancreatic adenocarcinoma and cholangiocarcinoma. Final determination of malignancy in biliary strictures can entail major surgery if pre-operative diagnosis of malignancy cannot be made. The surgical literature suggests that approximately 15–24% patients undergoing surgical resection for suspected biliary malignancy have benign etiology, but there are no clinical or radiological features to reliably distinguish benign from malignant biliary strictures. A pre-operative determination of malignancy is therefore highly desirable, to help plan appropriate treatment including the need for- and type of surgery.

It has always been a challenge to diagnose biliary malignany in view of difficult access for tissue sampling, no classical features on imaging and lack of a sensitive tumour marker. There is ample data on bile cytology, brush cytology, image guided /EUS guided but diagnostic yield is usually around 50-60%.We retrospectively analysed our data of biliary cytology in last 1 year to assess the diagnostic yield We also compared the utility of spyglass cholangioscopy plus spybite and conventional ERC plus brush cytology in last 10 cases of indeterminate biliary strictures

## METHODOLOGY

The present study was conducted in the Department of Gastroenterology, Gastrocare Hospital Bhopal. After the approval of protocol by the Hospital Ethics Committee and obtaining informed consent from the patient .

### Inclusion criteria

1. Age group: 38 - 65 years
2. BMI <35 kg/ $m^2$
3. American Society of Anesthesiologist (ASA) physical status I and II

### Exclusion criteria

1. Patients' refusal or inability to give informed consent.

2. American Society of Anesthesiologist (ASA) ≥3 physical status of either sex

**Study design:** Retrospective study

**Period of study:** The study was carried out from July 2016 to July 2017. [One year]

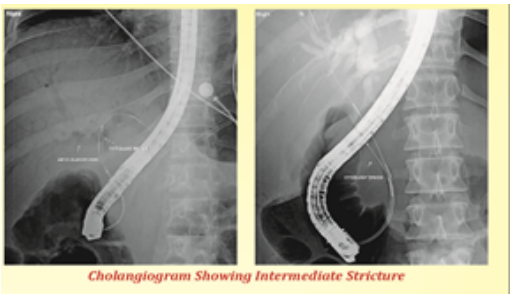
Overall 102 cases were referred for ERCP, out of which 15 had hilar block involving the confluence hence were taken up for PTBD, 4 had operable lesions and hence, were taken up for surgery and 5 had CBD stones masquerading as malignant stricture where CBD clearance was done. Rest 78 where ERCP was done formed the study group. This included 35 cases of Cholangiocarcinoma, 19 Gall bladder CA and 24 pancreatic tumors. In 48 patients, brush smears were taken for cytology; in 28 patients, bile was collected for cytology and in 2 patients, spy bite was taken.

We conducted a retrospective analysis of consecutive cases of malignant obstructive jaundice/ GB mass/ Pancreatic mass, based on imaging and subjected them to the appropriate cytological examination and CA 19-9 assays and compared them with clinical, radiological and surgical diagnosis.

## OBSERVATION TABLES

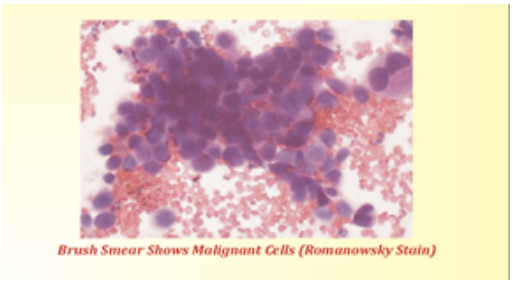
**TABLE 1: STUDY GROUP V/S CYTOLOGY GROUP**

| S. No. | Distribution of Various Malignanciesin Study Group | | Cytology Techniques | |
|---|---|---|---|---|
| 1 | Cholangiocarcinoma | 35 | Brush Smear | 48 |
| 2 | Cancer Gall Bladder | 19 | Bile for Cytology | 28 |
| 3 | Cancer Pancreas | 24 | Biopsy | 02 |
| | Total | 78 | Total | 78 |



Cholangiogram Showing Intermediate Stricture

**Fig 1: Cholangiogram showing sticture**



Brush Smear Shows Malignant Cells (Romanowsky Stain)

**Fig 2: Brush smear shwoing malignant cells**

## RESULTS

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The diagnostic yield was 61.5% (48/78). It was more for Brush smear (70%) as compared to Bile (50%). Spyglass cholangioscopy was suggestive of malignancy in 8/10, out of which spybite was taken in 2, both of which turned out to be positive. But we switched over to brush cytology as we found spy forceps difficult to use. CA 19.9 levels were available in 30 of 48 confirmed cases and were >500 in 20, between 100 & 500 in 2, between 30 & 100 in 6 and normal in 2. But CA 19.9 levels were also raised to >500 in 4/5 cases of CBD stones with cholangitis.

## STATISTICAL ANALYSIS:

Statistical analysis was done using Stata 11 software. Demographic characteristics, For continuous variables descriptive statistics (mean and standard deviations) were computed.. For categorical data chi-square test was applied. $P < 0.05$ was considered significant.

## DISCUSSION

It is known that yield of biliary cytology during ERCP is around 30-50 % in various studies. Factors which favour a positive results are older, age longer stricture and presence mass. Our study showed higher yield of brushings, probably because we take brush after dilation of stricture without injecting contrast (air cholangiogram guided) and that we have an onsite pathologist, CA 19.9 has been used by various studies and limitation is poor specificity especially in presence of cholangitis.

There are a multitude of nonoperative tools to evaluate indeterminate biliary strictures: tumor markers, cross sectional imaging, EUS-FNA, and a variety of ERCP-based techniques. Unfortunately, each has their advantages and limitations. As a result, a rational approach to their utilization is needed. Until that time, each patient with an indeterminate bile duct stricture requires a multidisciplinary approach with the goals of maximizing sensitivity for detecting malignancy in the most cost-effective manner.

In the study of Reddy SB, Patel T et al in which they have discussed about current approaches to the diagnosis and treatment of cholangiocarcinoma, ERCP is important in the diagnosis and management because tissue confirmation can be achieved with this technique. Brushings for cytology and biopsy samples for histology can confirm the diagnosis of cholangiocarcinoma. However, the sensitivity of these tests has been disappointing, ranging from 18% to 60%. Newer diagnostic tests, such as digital imaging analysis and fluorescence in situ hybridization, may offer increased sensitivity while maintaining the high specificity of cytology. Other techniques that use DNA-ploidy, such as flow cytometry, have been shown to improve the sensitivity of brush cytology while maintaining high specificity. However, these technologies are not routinely available nor are they uniformly validated.[2]

Charbel H, Al-Kawas FH et al did their work on cholangiocarcinoma and its epidemiology, risk factors, pathogenesis, and diagnosis. They inferrered that cholangiocarcinoma (CCA) is a rare tumor arising from the epithelium of the intrahepatic or the extrahepatic bile ducts. It is rarely diagnosed before 40 years of age except in patients with primary sclerosing cholangitis. CCA is usually clinically silent until the tumor obstructs the bile ducts. Carbohydrate antigen 19-9 is the most commonly used tumor marker, and magnetic resonance cholangiopancreatography is the best available imaging modality for CCA. Cholangioscopy and Endoscopic retrograde cholangiopancreatography allow tissue acquisition. Positron emission tomography may play a role in identifying occult metastases. Tissue diagnosis is obtained by brush cytology or bile duct biopsy.[1]

Jung GS, Huh JD et al did an analysis of percutaneous transluminal forceps biopsy in 130 patients suspected of having malignant biliary obstruction.The lesions involved the common bile duct (n = 58), common hepatic duct (n = 39), hilum (n = 14), ampullary segment of the common bile duct (n = 11), right or left intrahepatic bile duct (n = 5), or the entire extrahepatic bile duct (n = 3). In each

patient, three to five specimens (mean, 4.1 specimens) were taken from the lesion with 5.4-F biopsy forceps. The final diagnosis for each patient was confirmed with pathologic findings at surgery, additional histocytologic data, or clinical and radiologic follow-up. Sensitivity was significantly lower in the ampullary segment of the common bile duct than in other sites ($P < .01$). No major complications related to the biopsy procedures occurred.Their inference was that percutaneous transluminal forceps biopsy is a safe procedure that is easy to perform through a transhepatic biliary drainage tract. It provides relatively high accuracy in the diagnosis of malignant biliary obstructions.[2]

Awadallah NS, Chen YK et al investigated the role for cholangioscopy in patients with primary sclerosing cholangitis for 1) detection of cholangiocarcinoma using cholangioscopy-assisted biopsy 2) detection of stones not seen on cholangiography 3) stone removal with cholangioscopy-directed lithotripsy.They did a prospective cohort of consecutive patients referred for cholangioscopy to evaluate dominant strictures or stones. A data collection sheet was employed. Follow-up was by chart review/phone contact. Clinical improvement was defined as resolution of jaundice or ≥50% reduction in pain or cholangitis episodes requiring hospitalization. Stones detected by cholangioscopy were missed by cholangiography in nearly one of three patients.They concluded that cholangioscopy-directed lithotripsy may be superior to conventional ERCP for achieving complete stone clearance. Despite the use of cholangioscopy, diagnosis of cholangiocarcinoma remains technically challenging.[3]

Yeo D, Perini MV et al did their work on focal intrahepatic strictures. Focal intrahepatic strictures are becoming more common owing to more prevalent and accurate cross-sectional imaging. The purpose of the present review was to synthesize the current evidence regarding these lesions and to formulate a strategy for diagnosis and management.Most patients are asymptomatic while the minority present with vague abdominal pain or recurrent sepsis and only rarely with jaundice. Investigations used to distinguish benign from malignant aetiologies include blood tests (CEA, Ca19.9), imaging studies [ultrasonography (US), computed tomography (CT), magnetic resonance cholangiopancreatography (MRCP) and fluorodeoxyglucose-positron emission tomography (FDG-PET)], endoscopic modalities [endoscopic retrograde cholangiopancreatography (ERCP)/endoscopic ultrasound (EUS)/ cholangioscopy] and tissue sampling (brush cytology/biopsy). The authors concluded that a focal intrahepatic stricture requires thorough investigation to exclude malignancy even in patients with a history of biliary surgery, hepatolithiasis or parasitic infection. If all diagnostic modalities suggest a benign aetiology, then cholangioscopy with targeted biopsies should be performed.[9]

Early diagnosis of dysplastic changes and exclusion of cholangiocarcinoma (CCA) in patients with primary sclerosing cholangitis (PSC) remain a major clinical challenge. Although SpyGlass cholangioscopy (SOC) appears effective in diagnostics of indeterminate biliary strictures, Siiki A et al studied the role of cholangioscopy in the evaluation of primary sclerosing cholangitis-related biliary strictures. The aim of this study was to assess the clinical feasibility of SOC and directed biopsies, flow cytometry, and brush cytology in PSC patients**.** Brush sample and directed biopsies were successfully acquired from strictures in all cases. Samples were adequate for cytological and histological diagnosis in 9 (82%) and 10 patients (91%), respectively. There were two cases of pancreatitis. They concluded that SpyGlass SOC and directed biopsies seem to offer a feasible and promising method in evaluation of PSC-related strictures. [10]

Our results are comparable with the awailable litrature and moreover our sensitivity of brush cytology is higher than most available studies.This is probably because we take brushingsafter dilatation and also,we have an onsitecytologist.

Further studies are needed to clarify the role for new technologies such as cholangioscopy, cholangioscopy-directed biopsies, FISH, and advanced imaging techniques (eg, endomicroscopy, narrow band imaging). Because the diagnostic yield of a single intraductal brushing is so poor, should FISH, cholangioscopy, repeat (how many?) brushings, or some combination be routinely performed during the initial ERCP? In the current US health care system, the added costs of these technologies may be offset by improvements in the diagnostic yield of the first ERCP, thereby reducing the need for downstream tests. Similar to EUS-FNA where multiple passes improve the diagnostic yield, prospective studies evaluating the incremental benefit of 2 or more intraductal brushings during the initial ERCP are needed. Enhanced cross-sectional imaging and EUS may further limit the role for diagnostic ERCP but is unlikely to replace its therapeutic impact for effecting biliary drainage. The improved safety profile of laparoscopy should encourage gastroenterologists to obtain an expert surgical opinion early in the management of these patients; while sometimes we feel an obligation to confirm a tissue diagnosis before consultation, surgery may be the inevitable outcome

## CONCLUSION

There are a multitude of nonoperative tools to evaluate indeterminate biliary strictures: tumor markers, cross sectional imaging, EUS-FNA, and a variety of ERCP-based techniques. Unfortunately, each has their advantages and limitations. Brush cytology in our set up is a very good tool and yield is about 70% .Very high levels of ca 19.9 are suggestive but cannot be relied upon as a sole evidence of malignancy. Spyglass images strengthen the diagnosis of cholangiocarcinoma but spybite is not a practical tool as passage through spy scope is very difficult and time consuming . SpyGlass SOC and directed biopsies seem to offer a feasible and promising method in evaluation of PSC-related strictures. However, the long-term prognostic value it adds to cytology and flow cytometry remains to be assessed in future trials

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