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# Biliary Exfoliative Cytology- A Diagnostic Tool in Cases of Malignant Obstructive Jaundice

**Running Title: Biliary Exfoliative Cytology in Malignant Obstructive Jaundice**

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## A B S T R A C T

**Objective:** Malignant biliary strictures are a major cause of obstructive jaundice, often leading to poor survival if not diagnosed and treated early. Many patients require biliary drainage due to locally advanced or metastatic tumors. This study evaluates bile exfoliative cytology from endoscopic retrograde cholangiopancreatography (ERCP) and percutaneous transhepatic biliary drainage (PTBD) as a diagnostic tool.

**Design:** Histopathology, including FNAC and biopsy, is the gold standard for diagnosis. Bile cytology results from PTBD and ERCP were compared to tissue diagnoses to assess diagnostic accuracy.

**Results:** Among 81 subjects, 43 had gallbladder carcinoma, 24 had cholangiocarcinoma and 14 had periampullary carcinoma. Of these, 68 were confirmed malignant (54 by tissue diagnosis, 14 via PET-CT/tumor markers). In the PTBD group (68 subjects), 17 tested positives for malignant/atypical cells. In the ERCP group (13 subjects), 8 tested positive. ERCP yielded sensitivity of 80%, specificity 100%, PPV 100% and diagnostic accuracy 84.6%. PTBD showed sensitivity of 30.9%, specificity 100%, PPV 100% and diagnostic accuracy 44.11%.

**Conclusion:** Negative results does not exclude malignant disease, however, if positive, it is considered diagnostic (PPV 100%) and with minimal costs. This becomes more relevant when tumour is either locally advanced or metastatic and a tissue diagnosis is required to start either neo adjuvant or definitive chemotherapy. But tissue diagnosis along with tumour markers is costly, time

consuming, risky and cumbersome for the subjects. Henceforth biliary exfoliative cytology really serves the purpose in getting tissue diagnosis which can determine the course of management.

**Keywords:** Biliary Exfoliative Cytology; Malignant Obstructive Jaundice; Endoscopic Retrograde Cholangiopancreatography; Percutaneous transhepatic biliary drainage; Diagnostic tool

## Introduction

Malignant obstruction of biliary tree has a poor prognosis. In India one of the most common causes of malignant obstructive jaundice is Carcinoma Gall Bladder [CaGB]. CaGB is an aggressive and lethal cancer, with overall 5-year survival being only 10%. Ca GB is very common in gangetic belt of north India[1]. Advanced stages of CaGB continue to have dismal outcome with only anecdotal long-term survival[2].

Malignancy of the extrahepatic biliary tract encompasses cholangiocarcinoma, Ca GB, pancreatic adenocarcinoma, periampullary carcinoma and carcinoma head of the pancreas. Tumours in this complex anatomic location tend to present at more advanced stage and tissue diagnosis can be further delayed because of inaccessibility of the tumours to standard biopsy technique. The sensitivity of the tissue diagnosis obtained by different methods have low sensitivity. Time to diagnosis is especially important in these malignancies because surgical resection is the only treatment that offers survival advantage. Surgery is often not an option when disease is not locally confined[2].

So we prospectively made two ERCP/PTBD group who underwent the above mentioned procedures as part of their treatment of obstructive jaundice. We collected the bile in those subjects who underwent ERCP/PTBD procedures and analysed them to know the diagnostic efficacy of bile exfoliative cytology.

The incidence of gallbladder carcinoma varies in different parts of the world. It is the most common gastrointestinal malignancy diagnosed in North Indian women approximately 21.5/100,000 women in Delhi[3]. Most of the time treatment has been planned based on imaging only. To our knowledge, the potential use of bile cytology has remained largely unexplored, with only a few studies available to date in the literature[4]. Cytological features of precursor lesions of gallbladder carcinoma in bile obtained from surgically excised gallbladders have been described previously[5]. Bile or gallbladder contents contain cells exfoliated from the entire gallbladder mucosa and bile ducts; therefore, it was believed that cytological examination may be a good technique for the detection of early precursor lesions, even when they are focal or patchy in distribution[6].

All tumours which can cause the obstruction of biliary tract or ampulla of Vater can cause obstructive jaundice. Nearly 20% of these malignancies can be resected at the time of presentation. These tumours include cholangiocarcinoma, pancreatic cancer, cancers of the second part of duodenum and cancer of the ampulla of Vater[7]. The outlook from extra hepatic cholangiocarcinoma is also poor with a reported 5-year survival of 12%[8]. Therefore, accurate diagnosis of biliary strictures is beneficial in planning treatment and for giving information on prognosis, planning for neoadjuvant therapy in locally advanced disease and primary therapy in metastatic disease. Biliary brushing is currently regarded as the optimum method of obtaining cytological samples for analysis.

There are many causes of bile duct stricture and differentiating benign from malignant may be difficult, even in a specialized centre. History, physical examination and biochemical tests are usually unhelpful. Ultrasonography and computed tomography (CT) may establish the presence of biliary obstruction in more than 90 percent of subjects and are reasonably good at predicting the level of the obstruction with the sensitivity of ultrasonography being 60% and CT at 90%[9]. However, these imaging methods correctly predict the underlying pathology in only one-third (ultrasonography) to 80 percent CT of subjects[10]. As would be expected, the results are best for biliary obstruction caused by a pancreatic mass and worst for cholangiocarcinoma without a mass lesion. Although combining imaging methods may increase diagnostic accuracy, it remains below that required for making satisfactory clinical decisions and the preoperative imaging diagnosis is often incorrect[11].

By using pre-operative 18FDG-PET (Positron Emission tomography) scans, the sensitivity and specificity for intrahepatic versus extrahepatic malignant biliary lesions was at 95% and 100% versus 69.2% and 66.7% respectively. PET scans did show higher accuracy in showing regional & distant metastases[12,13].

An elevated CEA tends to be specific for gallbladder cancer (90%), but it lacks sensitivity (50%) when used as a screening test in cancer subjects compared with subjects who have benign gall- bladder diseases. CA19-9 is more consistent as a marker for gallbladder cancer, with sensitivities and specificities of approximately 75% at a level greater than 20 U/mL[14].

Carcino embryonic antigen (CEA) is widely used because of its availability but is elevated in only one third of subjects with cholangiocarcinoma[15,16]. CA19-9 is also widely used in the diagnosis of cancers of the upper GI tract and is elevated in gastric cancer, pancreatic cancer, biliary and gall- bladder cancers as well as in smokers, during cholangitis and in conditions causing cholestasis[17]. In addition, it is not present in 7% of the population who are Lewis A-antigen negative[18].

The addition of Endoscopic retrograde cholangio pancreatography (ERCP) and percutaneous transhepatic cholangiography (PTC) allow the site of a lesion within the biliary tree to be established but give little information about its nature[11]. Bile aspiration cytology of these cases yield almost 100 percent specificity though sensitivity is quite less[19] and with very minimal cost to the subjects. Most studies on the role of exfoliative cytology in these two scenarios have employed conventional cytological techniques. The introduction of liquid-based technology in the field of cytology lead to improved detection rates of malignancy in our study.

Hence, we planned to assess the usefulness of bile cytology in the diagnosis of CaGB with obstructive jaundice, periampullary carcinoma and cholangiocarcinoma.

## Aim

To analyse the diagnostic value of biliary exfoliative cytology in suspected cases of malignant obstructive jaundice.

## Materials and Methods

**Study design:** Prospective diagnostic study.

**Study location:** Study was conducted in Department of General Surgery, Medical

Gastroenterology & Cytology. PGIMER, Chandigarh.

**Study period:** 01.07.2013 to 30.06.2015

**Sample size:** 68 PTBD (Percutaneous transhepatic biliary drainage) + 13 ERCP

**Study population:** All clinically and radiologically suspected cases of malignant obstructive jaundice who underwent ERCP/ PTBD for their obstructive jaundice were included in the study as per inclusion and exclusion criteria. Informed consent was taken from all subjects. Ethical clearance from institute's ethics board was taken, Reference no. NK/1103/MS/13012-13.

**Inclusion criteria:** Informed consent.

All clinically and radiologically suspected cases of malignant obstructive jaundice irrespective of age.

Exclusion criteria: Subjects who refuse consent.

Prospective analysis of suspected cases of malignant obstructive jaundice

Cases of CaGB with obstructive jaundice, periampullary carcinoma and cholangiocarcinoma who underwent ERCP/ PTBD were enrolled prospectively from July 2013 to June 2015 and data was analysed for the demographic profile & malignant cytology of bile.

Subjects clinically and radiologically suspected to have gallbladder carcinoma; periampullary carcinoma & cholangiocarcinoma formed the study group. All the subjects who underwent PTBD & ERCP bile aspiration were included.

Most subjects with higher strictures not accessible by ERCP & failed ERCP subjects had undergone PTBD.

Approximately 50 mL of bile will be aspirated and collected in a sterile glass container. In subjects of pigtail biliary drainage samples of bile will be collected on post drainage day-0, day-3, & day-7. In subjects who underwent ERCP one sample will be collected at the time of procedure. Totally 68 PTBD and 13 ERCP samples were included in the study.

The bile sample reached cytology lab within 30 minutes of procedure.

Sample will be heparinised with 0.5ml of heparin and sent for malignant cytology as early as possible[20]. The bile samples will be processed in the Department of Cytology & Gynaec. Pathology. A proportion of the sample was centrifuged at 1500 rpm for 10 minutes and sediment smears were prepared and air-dried for MGG stain or ethanol-fixed for Papnicolaou stain. The remaining was fixed using the Cytorich fixative and processed for Liquid based Cytology [SurePath, Becton-Dickenson, India, Ltd.]. The manufacturer's instructions were followed. Both direct sediment smears and LBC preparation were evaluated for cellular details and a cytological diagnosis was provided which may be **(Figure 1)**.

Negative for malignant cells,

Atypical cells present,

Malignant cells present

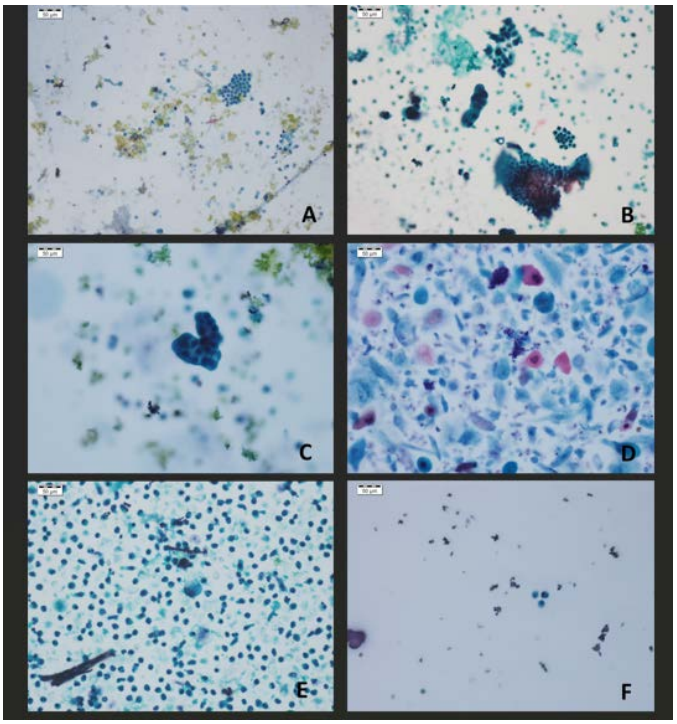


**Figure 1:** Bile Exfoliative Cytology, Liquid based Cytology preparations.

**A.** Benign epithelial cluster and greenish bile admixed with some inflammatory cells.

**B.** Malignant cell clusters showing nuclear pleomorphism from case of adenocarcinoma gall bladder.

**C.** Malignant cells in a papillary arrangement.

**D.** Malignant cells indicating Squamous cell carcinoma.

**E.** Occasional Atypical cell seen admixed with numerous neutrophils.

**F.** Occasional atypical cells in a case with very low cellularity. (Magnifications shown by scale bar, Papanicolaou stain).

**Compilation and tabulation of data:** Clinical details of all the cases was recorded in the enclosed proforma and finally entered in computer using data management software like MS excel or SPSS. Histopathology of the tumour/Tissue diagnosis which includes FNAC (Fine needle aspiration cytology) and Biopsy is considered gold standard in all subjects, bile aspiration cytology results namely atypical cells/malignant cells was held in comparison with the same in the end of the study. In subjects without tissue diagnosis PET CT12,13 or MRCP + Tumour markers were considered as gold standard[14,15].

**Statistical Analysis:** Quantitative data was presented as mean ± SD, categorical variables frequency & percentages were calculated. Chi-square test or Fisher's exact was applied for categorical data. Normality of quantitative data was checked by Box plot. Validity of ERCP biliary cytology was compared with Gold standard and Sensitivity, specificity, Positive predictive value, negative predictive value and diagnostic accuracy was calculated using SPSS version[17] (Statistical Packages for the Social Sciences, Chicago, IL). P value of $<0.05$ was considered as statistically significant.

## Results

Sex distribution among subjects: 50 females/ 31 males. Mean age among females being 51.7 years & in males 57.7 years.

Most common presenting complaint was jaundice followed by abdominal pain.

Among 68 patients who underwent PTBD, 43 patients had Ca gallbladder, 17 had Cholangiocarcinoma, 8 patients had Periampullary carcinoma (**Tables 1, 2**).

Among 13 patients who underwent ERCP, none of the patients had Ca gallbladder, 7 had Cholangiocarcinoma, 6 patients had Periampullary carcinoma (**Table 3**).

**Table 1:** The overall final cytology results of both PTBD & ERCP group combined is as follows.

| Benign | | Final diagnosis | | Total |
|---|---|---|---|---|
| | | Malignant | | |
| Cytology final | Negative | 16 | 40 | 56 |
| | Positive | 0 | 25 | 25 |
| Total | | 16 | 65 | 81 |

**Table 2:** The ERCP group yielded the following results.

| Benign | | Final diagnosis | | Total |
|---|---|---|---|---|
| | | Malignant | | |
| ERCP biliary cytology | Negative | 3 | 2 | 5 |
| | Positive | 0 | 8 | 8 |
| Total | | 3 | 10 | 13 |

**Table 3:** The PTBD group yielded the following results combining all the positive results of three sample sent.

| Benign | | Final diagnosis | | Total |
|---|---|---|---|---|
| | | Malignant | | |
| PTBD final | Negative | 13 | 38 | 51 |
| | Positive | 0 | 17 | 17 |
| Total | | 13 | 55 | 68 |

In the study it was observed that ERCP had better sensitivity, specificity, PPV, NPV and Diagnostic accuracy in diagnosing cases of malignant obstructive jaundice (**Table 4**).

**Table 4:** Comparison of sensitivity, specificity, PPV, NPV and Diagnostic accuracy between Overall, ERCP, PTBD at Day 0, 3, 7 and Final diagnosis.

| Parameter | OVERALL | ERCP | PTBD Overall | PTBD Day 0 | PTBD Day 3 | PTBD Day 7 |
|---|---|---|---|---|---|---|
| Sensitivity | 38.46% | 80% | 30.9% | 25.45% | 18.18% | 10.9% |
| Specificity | 100% | 100% | 100% | 100% | 100% | 100% |
| Positive Predictive Value | 100% | 100% | 100% | 100% | 100% | 100% |
| Negative Predictive Value | 28.57% | 60% | 25.4% | 31.7% | 28.8% | 26.53% |
| Diagnostic Accuracy | 50.6% | 84.6% | 44.11% | 39.7% | 33.82% | 27.94% |

## Discussion

Abdelghani et al[21]. told the number of cytological samplings ranged from 1 to 14 times. The cumulative diagnostic yield was 72.3% (34/47) and 32 positive results were obtained at a maximum of six samplings. In our study there was no significant advantage in sending multiple PTBD bile samples except for three cases which yielded positive results in second & third sample; with sensitivity and positive predictive value remaining almost the same as shown in the (**Table 4**) above.

The study by Wight et al[22]. review of 137 consecutive biliary brushings from 127 subjects by two experienced/dedicated cytopathologists improved the sensitivity from 49.4% to 89.0%, in line with previous studies. On review, 65 cases were reclassified as malignant when compared with 38 cases originally classified as malignant. In our study a total of four cases results were changed to malignant from atypical after review of slides. Overall Sensitivity increased from 33.84 to 38.4 %. The review of slides always yields improved positive results.

Atypical cells/malignant cells present in cytology results were considered as positive and compared with the gold standard in the analysis. There was a total of three cases (all three PTBD) reported positive for atypical cells.

Tumours such as cholangiocarcinoma are commonly sclerotic and there may be little exfoliation of malignant cells[23]. So the yield of tissue diagnosis in cases of cholangiocarcinoma is low as confirmed by our study.

Biliary strictures commonly present as obstructive jaundice. The aetiology of these strictures is usually neoplastic or inflammatory. Obtaining a histological diagnosis of the nature of these strictures is important to guide patient management and give information on prognosis, but can be difficult due to problems in getting adequate samples for pathology. ERCP & PTBD biliary exfoliative cytology is the method that provides the samples for pathological analysis[24,25]. However, this technique can have a low sensitivity with reported rates varying from 40% to 59.8%, although the specificity of this technique is reported to be high, with rates varying from 90.5% to 100%[22].

As we compared the final sensitivity of PTBD with previous PTBD studies sensitivity was low ranging from 20 to 60% while specificity being 100% in all.

As we compared the final ERCP results with previous ERCP studies sensitivity ranged from 50 to 80% and specificity remaining at 100%.

Obtaining tissue for diagnosis is difficult in the biliary tree but is essential to allow decisions to be taken on treatment and to assess prognosis; when obtained early it may obviate the need for subsequent investigation. Newer modes of treatment such as Liver transplantation for sclerosing cholangitis, balloon dilatation for benign biliary stricture and malignant stricture needing resection tells us the importance of having tissue diagnosis before proceeding with further management. Histological examination is impractical in most of the cases due to the location of tumours & in locally advanced tumours where chances of vascular injury are high[26].

Exfoliative cytology of bile samples obtained during ERCP and PTBD is remarkably safe, highly specific, easier and less invasive method to determine the diagnosis of suspected cases of malignant obstructive jaundice. Biliary strictures present a unique diagnostic challenge to clinicians as they can be caused by both benign and malignant conditions. The resectability rate of malignant obstructive jaundice is at 15-20 percent[27] of the total, hence this becomes more relevant when tumour is either locally advanced or metastatic and a tissue diagnosis is required to start either neo adjuvant or definitive chemotherapy.

Hence by quoting the above results and discussion, we could propose biliary exfoliative cytology has a definitive role to play in the patient's management in suspected cases of malignant

obstructive jaundice and we would like to recommend the excision of PTBD sites in cases where resection is feasible after drainage in view of our result[28].

## Drawbacks/Limitations

Despite the presence of a malignant biliary stricture exfoliative cytology can be negative for several reasons. Reasons being sampling error or the tumour may have produced a biliary stricture by external or intramural sclerosing compression of the biliary tract without producing ulceration of mucosa. Despite the application of biliary exfoliative cytology around 40-60 % of subjects remained without tissue diagnosis. PTBD samples yield low sensitivity compared to ERCP samples. This can be overcome by increasing the total number of samples sent and reviewing the slides by an expert[22].

As mentioned above[28] in the subjects who underwent PTBD had the risk of PTBD track seeding of tumour cells which may result in decreased resectability in subjects undergoing the same procedure.

## Conclusion

Bile withdrawn for cytology during ERCP and PTBD is a safe method with no increasing in patient's morbidity. As it is routinely done in subjects of malignant obstructive jaundice and allows a diagnostic orientation in more than 50% of the subjects.

Atypical cells added in positive results improve sensitivity and accuracy.

Negative results do not exclude malignant disease, however, if positive, it is considered diagnostic. (positive predictive value 100%).

Everybody must go through the complete medical history & radiological reports before confirming the malignancy. Multi-disciplinary team approach involving communication between the cytopathologist and the referring surgeon/gastroenterologist is essential to ensure clear understanding of the terminology used to render a diagnosis. The accurate interpretation of biliary tract brushings can be made by an experienced cytopathologist who have full knowledge of the diagnostic pitfalls.

With more than 30% PTBD cases being tested positive in biliary malignant cytology in our study; we also recommend the excision of PTBD catheter site during surgery as there is every chance of malignant cells seeding along PTBD track.

Hence, we conclude all the subjects suspected of malignant obstructive jaundice planned for ERCP/PTBD procedures should get their bile cytology samples sent for evaluation of malignancy. If cytology results are negative multiple samples can be sent or slides reviewed again by expert cytopathologist before being planned for interventional procedures for tissue diagnosis.

**Declaration of patient consent:** The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

## Conflicts of Interest

None.

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