

# A prospective controlled study comparing brush and bile exfoliative cytology for diagnosing bile duct strictures

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## Abstract

**Imaging of biliary strictures may suggest malignancy but cytology can provide a tissue diagnosis. The aim of this study is to compare the diagnostic value of brush cytology and bile cytology. Thirty two patients (20 males, 12 females, median age 66 years, range 31-84) with biliary strictures at endoscopic retrograde cholangio pancreatography (24) or percutaneous transhepatic cholangiography (8) had bile cytology and brush cytology. Brushings were taken using a modified Geenan cytology brush (6 Fr gauge, Wilson Cook) passed alongside a guide wire placed through the stricture. Bile was aspirated after insertion of an internal/external catheter or an endoprosthesis. Bile and brushings were examined by one experienced cytologist (AD) and was reported as positive or negative for malignant cells. Twenty nine patients had malignant strictures. Sixteen were confirmed by histology and 13 had malignancy suggested by clinical follow up. Three patients had resection of histologically benign strictures. The overall sensitivity of brush cytology (17 of 29 positive, 59%) was significantly greater than bile cytology (seven of 29 positive, 24%) ( $p < 0.01$ ) as was the diagnostic accuracy (63 v 31%,  $p < 0.01$ ). None of the patients had positive bile cytology with negative brush cytology. There were no procedure related complications and the average sampling time once the guide wire had been inserted was less than five minutes. It is concluded that brush cytology is more sensitive than bile cytology and with the technique described is safe and rapid.**

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The treatment options for patients with bile duct strictures range from endoscopic stenting or balloon dilatation to surgical resection or liver transplantation. Which treatment is most appropriate often depends on whether the stricture is benign or malignant and it is therefore inappropriate for patients to be managed without a tissue diagnosis. One of the safest and least invasive methods of obtaining a diagnosis is exfoliative bile cytology which has produced reliable results since the introduction of bile sampling at the time of endoscopic or percutaneous cholangiography. Although highly specific the sensitivity of exfoliative bile cytology is generally low.<sup>1,2</sup> Endobiliary brushes have recently been introduced which are reported to increase cell exfoliation and significantly improve results.<sup>3</sup> We have carried out a prospective controlled study to compare the results of bile

cytology with brush cytology in patients with bile duct strictures.

## Methods

### PATIENTS

Thirty two patients were studied prospectively. There were 20 men and 12 women with a median age of 66 years (range 31-84). All patients had biliary strictures demonstrated at endoscopic retrograde cholangiopancreatography or percutaneous transhepatic cholangiography. Of the 32 patients 29 had strictures thought to be the result of malignant disease (pancreatic cancer (16), bile duct cancer (nine), ampullary cancer (three) and metastases in (one)) and three were because of benign disease (sclerosing cholangitis, Mirizzi syndrome, and villous adenoma one each). The three patients with benign strictures all underwent surgery and had histological confirmation of benign disease. Of the 29 patients with malignancy histological confirmation was obtained in 16 patients. This was obtained from biopsies at operation, under ultrasound or computed tomography guidance, endoscopic retrograde cholangiopancreatography or percutaneous transhepatic cholangiography in eight patients, from resected surgical specimens in six patients and at necropsy in two. In 13 patients the diagnosis was based on the appearance of a malignant stricture at cholangiography along with an ultrasound and/or computed tomography scan evidence of a mass and disease progression leading to death (Table I).

All patients had brush and bile cytology performed during the same diagnostic procedure. The samples were collected by the gastro-

TABLE I Follow up of patients without histology

| Age | Sex | Diagnosis | Investigations      | Outcome    |
|-----|-----|-----------|---------------------|------------|
| 60  | M   | Mets      | US, CT, PTC         | Died 5/12  |
| 74  | M   | CCA       | US, CT, ERCP        | Died 1/12  |
| 41  | M   | Ca panc   | US, CT, Angio, ERCP | Died 1/12  |
| 56  | F   | CCA       | US, CT, Angio, ERCP | Died 3/12  |
| 70  | M   | Ca panc   | US, CT, ERCP        | Died 5/12  |
| 81  | F   | Ca panc   | US, CT, PTC         | Died 5/12  |
| 84  | M   | Ca panc   | US, CT, ERCP        | Died 6/12  |
| 76  | M   | Ca panc   | US, CT, ERCP        | Died 10/12 |
| 83  | F   | Ca panc   | US, CT, ERCP        | Died 4/12  |
| 82  | F   | Ca panc   | US, CT, ERCP        | Died 10/12 |
| 83  | F   | Ca panc   | US, CT, PTC         | Died 15/12 |
| 72  | M   | Ca panc   | US, CT, ERCP        | Died 6/12  |
| 40  | M   | Ca panc   | US, CT, Angio, PTC  | Died 6/12  |

M= male; F= female; Mets= liver metastases; CCA= cholangiocarcinoma; Ca panc= pancreatic cancer; US= ultrasound; CT= computed tomography; Angio= selective mesenteric angiography; ERCP= endoscopic retrograde cholangiopancreatography; PTC= percutaneous transhepatic cholangiography; /12= time in months.

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enterologist or radiologist carrying out the endoscopic retrograde cholangiopancreatography or percutaneous transhepatic cholangiography. Brush tips were removed and placed in 0.9% saline. The brush and bile were then immediately taken to the Cytology Department. The cells were washed from the brush and both samples centrifuged at 20 000 rpm for five minutes. The centrifuged deposits were then resuspended in 0.9% saline and cytospin slide smears produced by a low acceleration centrifuge. Four cytospin slides were then prepared from each specimen which were then stained with Papanicolaou and May Grunwald Giemsa.

#### PERCUTANEOUS TRANSHEPATIC CHOLANGIOGRAPHY

This was performed in eight of the 32 patients. Antibiotic prophylaxis was used in all patients (Mezlocillin 2 g iv, Bayer, Newbury, UK). After identifying the stricture by direct cholangiography using a 23 gauge Chiba needle (William Cook, Letchworth, Herts, UK) a guide wire was inserted into the biliary tree through a Surgimed sheath needle (Meadox, Dunstable, UK) and negotiated through the stricture into the duodenum. A peel off catheter (Miller, William Cook) was then inserted over the guide wire and positioned above the stricture. With the guide wire *in situ* the stricture was brushed through the catheter using a 6 Fr gauge Geenan cytology brush (Wilson Cook, Salem, USA). A Miller double mushroom (William Cook) or Carey Coons (Meditech, Watertown, USA) biliary stent (10-14 Fr gauge) was then inserted. Bile was collected at the end of the procedure once the stent was in position.

#### ENDOSCOPIC RETROGRADE CHOLANGIOPANCREATOGRAPHY

This was the sampling method used in the majority of patients (24 of 32). Antibiotic prophylaxis was used in all patients (Mezlocillin 2 g iv, Bayer, Newbury, UK). Endoscopic retrograde cholangiopancreatography was performed using Olympus TJF-10 or JF-IT10 scopes and a flexible tipped guide wire (William Cook) was negotiated through the stricture. Brushings were again taken using a 6 Fr gauge Geenan cytology brush (Wilson Cook, Salem, USA) which on this occasion was modified by the method suggested by Foutch *et al.*<sup>4</sup> Thus by piercing a hole in the tip of the sheath this could be passed up alongside the guide wire through the stricture. The brush within the sheath was then advanced and the sheath withdrawn sufficiently to allow brushing of the stricture while the guide wire remained across the stricture. As with the percutaneous procedure bile was aspirated after insertion of an endoprosthesis.

#### Results

All samples received by the cytology laboratory were cellular and satisfactory for analysis. The results were reported as positive or negative for malignant cells by a single experienced cytologist (AD) and the results were compared between

TABLE II Results of bile and brush cytology

|             | Bile cytology | Brush cytology |
|-------------|---------------|----------------|
| Sensitivity | 24% (7/29)    | 59% (17/29)    |
| Specificity | 100% (3/3)    | 100% (3/3)     |
| PPV         | 100%          | 100%           |
| NPV         | 12%           | 20%            |
| Accuracy    | 31%           | 63%            |

PPV = positive predictive value; NPV = negative predictive value.

TABLE III Sensitivity of cytology by cancer type

|                   | Bile cytology | Brush cytology |
|-------------------|---------------|----------------|
| Pancreatic cancer | 31% (5/16)    | 50% (8/16)     |
| Bile duct cancer  | 11% (1/9)     | 56% (5/9)      |
| Ampullary cancer  | 0% (0/3)      | 100% (3/3)     |

groups using a  $X^2$  test with Yates correction as necessary.

The results are shown in Tables II and III. Brush cytology was significantly more sensitive than bile cytology (59% *v* 24%) ( $p < 0.01$ ) and had a higher diagnostic accuracy (63% *v* 31%) ( $p < 0.01$ ). The sensitivities were not significantly different between the tumour types for either the bile or the brush cytology ( $X^2$  test). The specificity of both brush and bile cytology was 100%, accurately identifying all three non-malignant strictures. There were no false positive reports.

Brush cytology was positive in 10 patients with malignancy in whom bile cytology was negative. Conversely, none of the 12 patients with malignancy in whom brush cytology was negative was bile cytology positive. There were no procedure related complications and the time required for both brush and bile cytology sampling was less than five minutes once the guide wire had been negotiated across the stricture.

Of the 17 patients with positive brush cytology nine also had histological confirmation of the diagnosis from biopsies, surgically resected specimens or post mortem examination. In eight patients malignancy was suspected on the grounds of imaging and subsequent clinical outcome but cytology alone provided a tissue diagnosis. The overall rate of tissue diagnosis obtained in this series of patients with bile duct strictures (histology + cytology) was 27 of 32 (84.5%).

#### Discussion

This prospective controlled study has shown that brush cytology is positive in almost two thirds of patients with malignant biliary strictures (59%) whereas bile cytology is only positive in approximately one in four (24%). The results for the bile sampling is similar to those reported by Pugliese and colleagues<sup>1</sup> but is lower than that achieved by some others.<sup>2,5</sup> There is less variability between the results reported for brush cytology with most groups reporting a sensitivity of about 60% which is similar to that found in the present study.<sup>1,3,4,6</sup> In general the results reported for bile exfoliative cytology<sup>1,2,5</sup> show a lower sensitivity than for brush cytology<sup>1,3,4,6</sup> although the patient groups in these studies are unlikely to be comparable. The single prospective controlled study

which has previously compared bile and brush cytology investigated 30 patients with bile duct strictures (17 malignant and 13 benign).<sup>7</sup> Foutch<sup>7</sup> reported a sensitivity of 6% for bile cytology (one of 17) as compared with 35% (six of 17) for brush cytology. These reported sensitivities are considerably less than those generally reported.<sup>1-6</sup> This low sensitivity of bile cytology may be explained by the bile sampling being performed before brushing or stenting. We carried out bile sampling after these invasive procedures which possibly increased cell exfoliation. Although the results of brush cytology were better than those of bile cytology in Foutch's study these differences were not statistically significant (six of 17 *v* one of 17,  $X^2=ns$ ). In contrast our study has clearly shown that brush cytology is significantly better than exfoliative bile cytology for establishing the nature of bile duct strictures. An important point is that none of the patients with negative brush cytology had positive bile cytology. This would suggest that bile sampling is unnecessary when brushings have been performed.

No false positive results were found in the present study resulting in a test specificity for bile and brush cytology of 100%. Although this is based on only three patients with benign strictures most other series on either bile or brush cytology have also reported no false positive results.<sup>2-4</sup> This allows patient management to be safely based on the cytological finding of neoplastic cells.

The method used for obtaining samples by endoscopic brush cytology has major implications for routine clinical practise. The Foutch method was described in 1989 and allows endobiliary brushing without removal of the guide wire inserted across the stricture.<sup>4</sup> Before this development the guide wire had to be removed before brushing and reinsertion of the guide wire was often difficult or impossible. The difficulty and time involved for this procedure was therefore prohibitive in contrast with the Foutch method used in the present study which required a sampling time of less than five minutes once the guide wire had traversed the stricture. In addition there were no procedure related complications in this group of patients, again a finding reported by Foutch and colleagues.<sup>4</sup>

The results of the present study would suggest that brush cytology is able to diagnose about two thirds of patients with extrahepatic bile duct obstruction. Whether this figure could be improved with repeated brushings was addressed by Rabinowitz and colleagues in 1990 in patients with suspected bile duct cancer. It was clearly established that repeated brushings increases the

diagnostic accuracy of brush cytology and that after three negative endobiliary brushings the chance of a stricture being due to a cholangiocarcinoma was calculated to be less than 6%.<sup>8</sup> The findings of this study are of major importance in certain circumstances, such as in patients with biliary strictures caused by primary sclerosing cholangitis who are predisposed to the development of cholangiocarcinomas and who are otherwise suitable candidates for liver transplantation.

Although repeated brushings increases the diagnostic sensitivity in patients suspected of cholangiocarcinoma a similar study has not been performed in patients with distal bile duct strictures and the potential of biliary brush cytology for the overall diagnosis of bile duct strictures has not, therefore, been established. Repeated brushing is unlikely to diagnose biliary strictures which are the result of extrinsic compression on the biliary tree by malignancy unless there is bile duct invasion and in this group of patients combining brush cytology with other diagnostic means such as percutaneous fine needle aspiration cytology<sup>9</sup> or the more recent developments of endobiliary biopsy forceps<sup>10</sup> or endobiliary fine needle aspiration cytology<sup>11</sup> should be investigated.

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