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RAPID COMMUNICATION

Biliary brush cytology: Factors associated with positive yields on biliary brush cytology

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Abstract

AIM: To evaluate the yield of brushing biliary strictures and the factors associated with a positive result in biliary strictures.

METHODS: Data on all consecutive patients (01/02 -10/05) who were identified to have a biliary stricture and who underwent biliary brush cytology were collected. The yield of positive biliary brush cytology was evaluated and compared to results with the gold standard for diagnosis (defined as either definitive surgical histology or clinical course). Additionally, associated factors of positive results including stricture location, gender, age, mass size, length of stricture, and dilatation prior to brushing cytology were assessed.

RESULTS: From 199 patients who had brushing cytology samples (10 patients were excluded due to lack of gold standard diagnosis), 77 patients had positive brushing cytology (yield 41%). Variables associated with positive cytology brushing on initial endoscopic retrograde cholangiography were age 1.02 (1.00-1.05), mass size > 1 cm 2.22 (1.01-4.89) and length of stricture > 1 cm 3.49 (1.18-10.2). The sensitivity of biliary brushing was 61%, its specificity 98%, the positive predictive value reached 99%, and the negative predictive value was 57%.

CONCLUSION: Our results revealed a 41% positive yield from brushing cytology. The sensitivity of biliary brushing cytology in our center was 61% and the specificity was 98%. Predictors of positive yield include older age, mass size > 1 cm, and stricture length of > 1 cm.

Key words: Biliary; Endoscopic retrograde cholangiopancreatography; Pancreas; Gallbladder; Ampulla

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INTRODUCTION

Biliary duct strictures are most often caused by neoplastic or inflammatory processes involving the biliary tree, pancreas, gallbladder, or ampulla. The use of endobiliary brush cytology to definitively diagnose malignant biliary strictures has been shown to be useful during endoscopic retrograde cholangiography (ERC). However, the diagnostic yield of this technique remains low, ranging from 30% to 80%[1-14] depending on the literature reviewed. Conservative management with biliary drainage is used in many patients with malignant tumors, most of whom are not candidates for curative resection due to locally advanced or metastatic disease. In such patients, an accurate tissue diagnosis may help in developing a concept for further management[3,4,15,16].

Cytological techniques have become the initial diagnostic modality in many cases since biliary lesions are not always readily accessible to biopsy[4,6,7,17]. Percutaneous radiologically guided fine needle aspiration (FNA), although a very accurate technique, is operator dependent and requires a sufficiently distinct mass lesion for targeting. Additionally, in patients who are surgical candidates 'seeding' of the needle tract has been a concern. Brush cytology performed at ERC, in contrast, has a low complication rate and allows sampling from most sites within the biliary duct systems[4,6,7,17].

The objective of this study was to assess the accuracy of brush cytology in biliary strictures and to assess the factors influencing results over a 3.7 years period from January 2002 to September 2005.

MATERIALS AND METHODS

From a total of 2500 endoscopic retrograde cholangiopancreatography performed between January 2002 and September 2005 at our center (St. Paul's Hospital, Vancouver), all biliary brush cytology findings were reviewed. This hospital serves as a tertiary referral center for the management of biliary diseases, and clinicians obtained follow up on all their patients. Two

hundred and ninety nine specimens were received, from one hundred and ninety nine patients in the review period. For inclusion in the study, patients had to have a definite final benign or malignant diagnosis based either on histological or cytological sampling or by clinical outcome. The latter was obtained by case record review. A total of ten patients (3.3%) were excluded from performance characteristics of endoscopic retrograde cholangiopancreatography (ERCP) brush cytology due to lack of gold standard for diagnosis.

Ethics approval for the chart review was performed through St. Paul's Hospital, University of British Columbia, Vancouver, Canada.

The specimens were obtained at ERCP with a Cytomax2, single use, 8 french, 2.5 cm long double lumen Wilson-Cook cytology brush (#4900 Benthania, Station Road, Winston-Salem, NC 27105). Fluoroscopic guidance ensured that the brush was within the stricture. Between ten and fifteen "in and out" passes with the brush was routinely used to ensure an adequate sample, and then the entire brush excised into formalin or saline and sent to the laboratory. Routine cytospin preparations were prepared and stained according to Papanicolaou's method. Samples were classified cytologically as follows: Class 1: Benign; Class 2: Reactive; Class 3: Suspicious for malignancy; Class 4: Cells with cancer morphology recommend biopsy (likely malignant but rarely can be reactive); Class 5: Malignant (equal to tissue diagnosis).

In our study definitively positive biliary brush cytology is defined as class 3 or higher.

Biliary duct stricture location was classified according to one thirds of total biliary duct length and was analyzed *via* two methods (apriori decided), once combining middle and lower common duct and once dividing the duct system to three equal parts. Other factors evaluated include length of stricture, mass size in CT scan/ultrasound, stricture dilation before brushing, age, and gender.

Statistical analysis

Descriptive statistical analysis with the calculation of means and standard deviations of the entire brushings cohort was carried out. Demographic variables were determined a priori as important factors in the outcome of the brushings. For categorical variables, a reference value was selected with the calculated odds ratio relative to the selected reference. Once significant variables were identified by univariate logistic regression analysis, a multivariate logistic regression was carried out. Sensitivity and specificity were calculated based on the gold standard of either surgical resection or clinical follow-up. All statistical analyses were carried out using Stata 8.0 (College station, TX).

RESULTS

Patient characteristics

A total of 199 patients met the inclusion criteria for the study. Ten patients with unknown final diagnoses were excluded. Findings from the remaining 189 patients were analyzed. The mean age was 66.3 (range 21-92) with 51.3% female. One hundred and twenty four patients (62.3%) had malignant and 65 (33%) benign strictures. Seventy seven (40.7%) of the biliary brushings were scored as class 3 or higher (i.e. malignant) and 112 (59.3%) as class 2 or lower (i.e. benign).

Cytological brushing confirmation was obtained in 62% (77/124) of patients with malignant strictures; however in the remaining 48 patients either FNA, surgical specimen or clinical course confirmed the malignant nature of the biliary stricture. Sixty-five patients had pancreatic adenocarcinoma, 10 had hepatic cancer, 16 had distal cholangiocarcinoma, 10 had presumed primary duodenal cancer, 4 had gallbladder cancer, and 3 had Klatskin tumor. The precise type of primary cancer was not identified in 16 patients, however, in all of them it was presumed to be pancreaticobiliary.

There was one non-neoplastic, false positive diagnosis. The patient was an 83-year-old man with a history of primary sclerosing cholangitis who developed a lower common duct stricture. Second brush cytology and ampullary biopsy however, revealed only reactive and inflammatory biliary epithelial changes. This patient was not subjected to surgery and is well 8 years later.

Sixty five patients had benign disease, most commonly strictures secondary to biliary stones (n = 38) and presumed sphincter spasm (n = 7). The rest had variety of benign diagnoses including primary sclerosing cholangitis (n = 4), chronic pancreatitis (n = 5), recurrent pyogenic cholangitis (n = 2), autoimmune liver disease, sarcoidosis, complex benign hilar stricture, leiomyoma, and anastomosis stricture.

Thirty six patients had repeat ERCP and brushing cytology from a period of one to ten months after initial negative cytology result. In 29 patients results of repeat cytology remained negative, however, seven patients were declared to have malignant stricture in repeat cytology. Adding the second cytology result to previous data led to an increase in sensitivity to 67% (83/124).

Overall, there were 76 true positive diagnoses, 64 true negative diagnoses, 48 false negative diagnoses, and one false positive diagnosis. The diagnostic sensitivity, specificity, PPV, and NPV of brush cytology for the series were 61%, 98%, 99%, and 57%, respectively.

Factors associated with positive yield

Among all variables studied including age, gender, location of stricture, CT scan findings, length of stricture, and endoscopic dilation prior to biliary brushing (Table 1), only age, mass size > 1 cm, and stricture longer than 1 cm are associated with positive cytology brushings. Variables associated with positive cytology brushing are illustrated in Table 2.

DISCUSSION

The examination of brush cytology is an established diagnostic technique in the investigation of patients with biliary strictures with suspected pancreatic, bile duct, ampullary, and gallbladder cancers. Acquisition of malignant cells by endoscopic brush cytology during initial ERCP is valuable in planning appropriate therapy and may be important for avoiding additional invasive procedures

Table 1 All variables studied for positive cytology brush

Variable	Value
Age (yr, range)	66.3 (21-92)
Gender (female)	51.30%
Location of stricture	
Lower CD	124
Mid + Upper CD	63
No stricture	12
CT scan findings	
CT not done	35
Mass not seen	95
Mass < 1 cm	5
Mass 1-3 cm	39
Mass > 3 cm	25
Length of stricture	
No defined stricture	14
Stricture < 1 cm	30
Stricture 1-3 cm	125
Stricture > 3 cm	30
Endoscopic dilation prior to brushing	15%
Final diagnosis	
Benign	65
Malignant	124
Unknown	10

CD: Common duct.

Table 2 Variables associated with positive cytology brushing

Variable	Odds ratio (95% CI)
Age	1.02 (1.00-1.05)
CT scan findings	
Mass < 1 cm	1
Mass 1-3 cm	2.22 (1.01-4.89)
Mass > 3 cm	2.86 (1.07-7.64)
Length of stricture	
Stricture < 1 cm	1
Stricture 1-3 cm	3.49 (1.18-10.2)
Stricture > 3 cm	7.70 (2.15-27.5)

for tissue diagnosis. We have reviewed brush samples from 199 patients during a time period of almost 4 years for yield, sensitivity, and specificity. This is one of the largest series of biliary brush cytology specimens reported and the largest and broadest study looking at factors associated with positive brush result.

The diagnostic sensitivity of biliary brushing has been relatively modest in most studies to date. Stewart and colleagues reviewed 406 patients and found the overall sensitivity to be 59.8%[13]. Similarly, Kurzawinski and colleagues[7,17] reviewed six early series and found the mean sensitivity to be 59%. However, two other large studies on brush cytology have recorded sensitivities of 35%-48% in the patients with pancreatico-biliary malignancy[5,8].

There are very few studies evaluating the factors influencing positive results. McGuire and colleagues have documented the association between the yield of enteropancreatic brush cytology and the location of malignancy, such that strictures of the head and body yielded higher rates of positive cytology compared to the strictures of ampulla, pancreatic genu, and tail regions[9]. DeBellis and colleagues have shown that stricture dilation does not improve the sensitivity of brush cytology for the detection of cancer. However, repeated brushing appears to increase the diagnostic yield[1].

We found that brush cytology accurately identified 76 of 124 (61.2%) neoplasms in our series, a similar result to those of earlier studies reviewed by Stewart and colleagues[13], Kurzawinski and colleagues[7,17], and by Foutch *et al*[3,4,18]. When we consider a second brushing in some patients our sensitivity increases to almost 70%. This is among the highest sensitivity reported in the literature. Other studies such as Lee *et al*[19,20], Ponchon *et al*[21], Longo *et al*[8,22], and Macken *et al*[23] all had lower sensitivities at 37%, 35%, 48%, and 57%, respectively. The reasons for the varied sensitivity are unclear.

Previous studies have shown that a diagnosis of carcinoma on brush cytology is highly specific. The specificity of biliary brush cytology in previous studies has been reported to be between 90%[17] to 100%[3,16,18,24-28]. There was one false positive diagnosis in our study (specificity 98%) in a patient with primary sclerosing cholangitis. Stewart and colleagues also reported three false positives cytological diagnoses among one hundred and sixty patients (specificity 98.1%)[13]. Sturm and colleagues also reported specificity of 97.2% with two false positive cytological diagnoses among 74 patients with benign strictures[30].

It has been suggested in previous studies that the limited sensitivity of brush cytology may be due to an inadequate cellular yield. Theoretically, stricture manipulation may increase exfoliation of tumor cells, making these cells more available for histopathologic evaluation, but DeBellis and colleagues have shown that stricture dilation does not improve the sensitivity of brush cytology for detection of cancer. In their study, brush cytology had a sensitivity of 34.5% before dilation and 31% after dilation ($P = 0.54$)[1]. On the other hand, Mohandas *et al*[31] found that dilation before bile aspiration improved the cancer detection rate of bile cytology. In their series, cytology was positive in 27% of cases without biliary stricture dilation compared to 63% when the stricture was dilated ($P < 0.03$). Use of scraping brush in the series reviewed by Parasher and Huibregtse[16] achieved a sensitivity of 100%. However, stricture dilation did not improve the diagnostic yield of brush cytology specimen in our series of 31 patients who had dilation prior to brush cytology OR 1.18 (0.48-2.85).

We have not routinely performed biliary aspiration or biopsy technique biopsies of the biliary tree; both of which may enhance diagnostic yield. Using a combination of simple biliary brushings occasionally with a second brushing combined with endoscopic ultrasound staging (and biopsy where required) sensitivity reaches more than 90%. Only a small selected group remains undiagnosed through the above two methods, and thus the benefit of other techniques (i.e. aspiration, endoscopic biopsy at ERCP) in increasing the yield is marginal in our hands.

We also analyzed positive yield for multiple factors including age, gender, location of stricture, mass size in CT scan or ultrasound, and the length of stricture. From all the mentioned variables positive brush result was associated with older age: 1.02 (1.00-1.05), mass size of more than 1 cm: 2.22 (1.01-4.89) and stricture longer than 1 cm: 3.49 (1.18-10.2).

In summary, in this study brush cytology identified 76 of 124 (61.2%) of neoplasms in a series of 199 consecutive patients evaluated during a 3.7 years period in our institution. One false positive cytological diagnosis occurred. From all the variables studied only age, length of stricture, and mass size in CT scan or ultrasound were associated with a higher yield. Gender, dilation of stricture prior to cytological sampling, or location of stricture were not found to be associated with a higher yield. Although the limitations of this technique must be recognized,, brush cytology is useful in investigation of patients with suspected biliary neoplasm. The challenge for future developments in this field is to develop strategies to improve lesion targeting facilitating retrieval of cytology specimens with higher quality.

COMMENTS

Background

The usage of biliary brushings has high specificity and moderate sensitivity in the diagnosis of malignant biliary obstruction. Although other methods of diagnosing the etiology of the obstructive lesion have become available we have evaluated our biliary tract brushing results to determine the sensitivity, specificity, and factors that might be associated with a positive result.

Research frontiers

Percutaneous biopsies have the risk of 'needle-track' seeding and thus are discouraged in patients deemed to be surgical candidates. Tissue from biliary/pancreatic lesions is also obtained through endoscopic ultrasound. We have not routinely used biliary aspiration or bile duct biopsies; both of which have a yield that may not be as high as reported in our study with biliary tract brushings.

Innovations and breakthroughs

We found that initial brush cytology accurately identified 76 of 124 (61.2%) patients with malignant biliary strictures. When a second brushing was performed in several patients, we obtained a sensitivity of close to 70%. This is much higher than most studies have reported. Theoretically, stricture manipulation may increase exfoliation of tumor cells, making these cells more available for histopathologic evaluation. Stricture dilation did not increase the yield. We also analyzed positive yield for multiple factors including age, gender, location of stricture, mass size in CT scan or ultrasound, and the length of stricture. From all the mentioned variables positive brush result was associated with older age: 1.02 (1.00-1.05), mass size of more than 1 cm: 2.22 (1.01-4.89), and stricture longer than 1 cm: 3.49 (1.18-10.2).

Applications

In this study, without the use of EUS, we still obtained a sensitivity of malignancy for biliary tract strictures of almost 70%. In this study we used Class 3 as a 'cut-off' for malignancy, however, some studies have used even more stringent criteria. When one then 'adds in' additional cytobiological results obtained with availability of EUS then the need for other methods to diagnose these lesions is limited to a very small group of patients.

Terminology

Biliary brushing: the use of a cytology brush through an endoscope to obtain samples for analysis. Biliary dilation: the use of either a step dilator or a balloon dilator to increase the size of the biliary tree lumen and to allow further intervention or to improve biliary flow.

Peer review

This is an important optimistic report on the diagnostic value of brush cytology in biliary strictures. The diagnostic yield is higher than it was reported in other previous studies. One additional aspect is the evaluation of factors influencing the results.

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