Diagnostic Value of Endoscopic Transampullary Biopsy for Malignant Bile Duct Stricture

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Abstract

Bile duct stricture, either benign or malignant, usually presented with jaundice, is a common surgical condition. Clinically the diagnosis is made empirically on the basis of clinical data and a telltale cholangiogram without histologic confirmation. Benign stricture, therefore, might be misinterpreted as malignancy. To obtain tissue confirmation, endoscopic transampullary biopsies were performed in 32 patients with clinically suspected malignant biliary stricture, between August 1997 and July 1998. Of these 32 patients, 16 patients each had biopsy-positive and biopsy-negative for malignancy. In the 16 biopsy-positive patients, 11 underwent exploratory laparotomy, and the other 5 did not. Of the 11 who were explored, 8 had histology confirmed malignancy, surgical biopsy was not feasible in the 3 remaining patients. The 5 patients who were not explored, all died within 5 months after the diagnosis was made. In the 16 biopsy-negative patients, 9 underwent exploratory laparotomy, of which 4 had malignancy confirmed histologically, 2 had no malignancy by histology but subsequently had clinical evidence which suggested malignancy, in the 3 remaining patients surgical biopsy was not feasible, however, their clinical courses suggested a benign condition. Of the 7 patients whose transampullary biopsies were negative, and who were not explored, 5 had a clinical course and evidence suggesting malignancy, of these 5 patients 4 died 1, 2, 3 and 10 months after the diagnosis, and one was lost to follow-up. The 2 remaining patients who had no clinical evidence of malignancy remained alive even 2 years after the follow-up.

Of the patients who underwent exploratory laparotomy and surgical biopsy, the sensitivity, specificity, positive predictive value and negative predictive value for transampullary biopsy were 66.7 per cent, 100 per cent, 100 per cent and 31.3 per cent respectively. There were no major complications related to transampullary biopsy per se.

The results suggested that transampullary biopsy is an effective and safe procedure for diagnosing malignant bile duct stricture.

Key word : Endoscopic Transampullary Biopsy, Malignant Bile Duct Stricture, Diagnostic Value

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J Med Assoc Thai 2000; 83: 992-998

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Most patients with bile duct stricture present with painless progressive jaundice. The important issue for this condition is to find the precise location and nature of the obstruction[1,2]. There are many causes of bile duct stricture and differentiating benign from malignant may be difficult. History, physical examination and biochemical tests are usually unhelpful. Ultrasound and computed tomography may establish the presence of biliary obstruction in over 90 per cent of patients and are good at predicting the level of the obstruction[3]. Endoscopic retrograde cholangiopancreatography (ERCP) and percutaneous transhepatic cholangiography (PTC) are also used to demonstrate the exact site of a lesion within the biliary tree. However, these imaging methods do not provide underlying pathology to allow a final diagnosis[4]. Malignant strictures of the bile duct can be difficult to discern from benign conditions. Verbeek et al reported a false-positive diagnosis of malignancy in 13.4 per cent of 82 patients of whom preoperative and perioperative diagnoses were hilar cholangiocarcinoma. In these cases the diagnoses were benign fibrosing disease[5]. Wetter et al also reported 31 per cent misdiagnosis in patients whose preoperative diagnosis was Klatskin tumor[4].

Preoperative tissue diagnosis of bile duct stricture is therefore highly desirable to facilitate proper therapeutic planning and accurate prognosis. This is particularly important when imaging techniques do not detect a mass lesion. However, tissue confirmation of malignancy is difficult to obtain [6-8]. Some authors advocated sampling tissue during ERCP as the first-line approach to tissue diagnosis of biliary stricture[6,9]. Some also advocated endoscopic forceps biopsy[10,11], however, complications from forceps biopsy have not been studied well. The aim of this study was to evaluate the effectiveness and safety of endobiliary forceps biopsy in patients with bile duct strictures.

PATIENTS AND METHOD

Patients who were suspected of having bile duct obstruction based on clinical findings, blood chemistries, ultrasound, or/and CT scan were investigated with ERCP during August 1997 and July 1998. ERCP was performed by two endoscopists with a standard technique using JTF 140 or JTF 130 Olympus duodenoscope. When cholangiogram confirmed bile duct stricture, endoscopic transampullary forceps biopsy (Fig. 1, 2) was performed after sphincterotomy, using a technique that has been previously described[12]. Strictures associated with common bile duct stones or ampullary tumor were excluded from this study. Ampullary tumor could be directly visualized and biopsied without sphincterotomy. From each patient, two to three biopsy samples were taken. Biopsy specimens were fixed in 10 per cent formalin solution, embedded in paraffin, stained with hematoxylin and eosin before

Fig. 1. Proximal bile duct forceps biopsy.

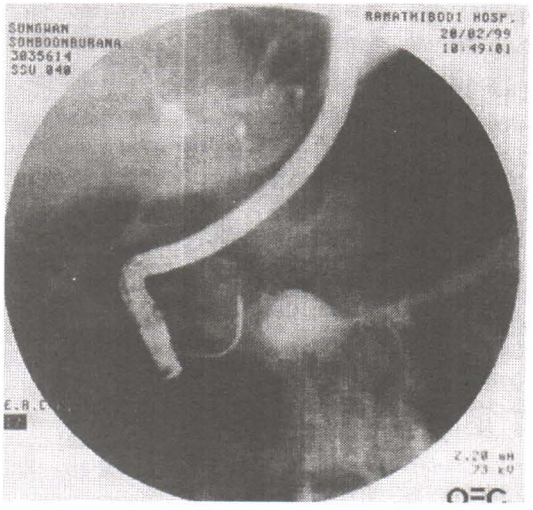

Fig. 2. Distal bile duct forceps biopsy.

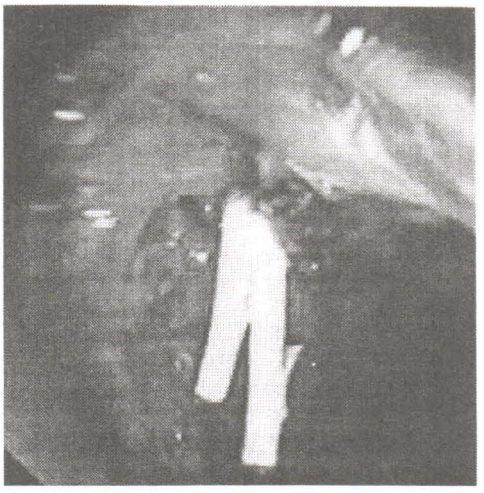

Fig. 3. Biliary (double) endoprosthesis.

being examined by the pathologist. For palliative reasons endobiliary prostheses were inserted in some patients after the biopsy (Fig. 3).

In this study, the final diagnosis was based on an additional histologic specimen from subsequent surgery or, when this was not possible, it was based on additional clinical, laboratory, and radioimage findings. Patients who had unexplained ascites, elevated tumor markers such as CA 19-9 or CT scan showing evidence of regional lymph nodes or distant metastasis were diagnosed as malignant bile duct stricture. In patients whose tests were negative for malignancy, and who remained well during follow-up were considered as non-malignant.

Sensitivity (percentage of biopsy specimens considered positive in patients with proven malignant disease); specificity (percentage of biopsy specimens considered negative in patients free of malignant disease); positive predictive value (percentage of times a positive biopsy specimen result would detect a patient with malignancy); negative predictive value (percentage of times a negative biopsy specimen result would detect a patient without malignancy) were calculated. Failure to obtain adequate forceps specimens were all regarded as negative studies.

RESULTS

During the study period, 32 patients underwent transampullary biopsies. The characteristics of the patients are shown in Table 1. There were 21 men and 11 women with a mean age of 57.6 years (range 35 to 81). The leading symptoms were obstructive jaundice, abdominal pain and ascending cholangitis. Biliary prosthesis was inserted after transampullary biopsy in 11 patients. The mean length of hospital stay was 9.5 days. There were 24 patients with proximal bile duct obstruction, 1 mid-duct obstruction, and 7 distal duct obstruction. Among these 32 patients, 4 had bile duct resection or/and hepatectomy, 8 had biliary-enteric bypass and 6 had external tube drainage.

The histological results of transampullary biopsy are shown in Table 2. Sixteen patients were positive for malignancy and the other 16 patients were negative. Among the 16 biopsy-positive patients, 11 patients were subsequently explored but

Table 1. Characteristics of the studied patients.

Characteristic	No.
Number of patients	32
Men / women	21 / 11
Mean age : years (range)	57.6 (35-81)
Stent insertions	11
Presenting symptoms	
Jaundice	17
Abdominal pain without jaundice	10
Ascending cholangitis	5

Table 2. Histology of transampullary biopsy specimens.

Pathological results	No. patients
Positive transampullary biopsy:	
- Adenocarcinoma	15
- Adeno- squamous carcinoma	1
Total	16
Negative transampullary biopsy:	
- No evidence of malignancy	4
- Dysplasia	4
- Chronic inflammation	3
- Inadequate tissue	2
- Normal mucosa	2
- Atypical epithelial cell	1
Total	16

Table 3. Results of transampullary biopsy (TABx) compared with surgical histology.

	Positive surgical histology	Negative surgical histology	Total
Positive TABx	8	0	8
Negative TABx	4	2	6
Total	12	2	14

Table 4. Results of negative transampullary biopsy (TABx) patients.

	Clinical diagnosis	
	Malignant	Benign
Surgical histology		
Malignancy	4	-
Benign	2	-
No surgical specimens	5	5
Total	11	5

surgical specimens could be obtained in only eight cases, all of which had malignancy confirmed histologically (Table 3). In the remaining 3 patients, surgical biopsy was not feasible, however, biliary drainage was performed in all 3. Exploratory laparotomy was not performed in 5 patients due to advanced disease or they refused surgery. Of the 8 transampullary biopsy positive patients who had no surgical confirmation, all had clinical evidence of malignancy and died within 6 months of the diagnosis.

In the 16 biopsy-negative patients, 9 patients were explored. Surgical biopsy could be performed in 6 patients of which 4 had malignancy histologically (Table 3), 2 had no malignancy (opisthorchiasis and chronic biliary inflammation), however, both died 4 and 6 months later with clinical evidence of malignancy. In the remaining 3 patients surgical biopsy was not feasible, however, they survived from 8 to 22 months during the follow-up without clinical or laboratory evidence of malignancy.

Among the 7 transampullary biopsy-negative patients who were not explored, malignancy was diagnosed in 5 patients; 4 of the 5 patients had hepatic mass, and one had pancreatic mass on CT scan during the follow-up. In one of the 4 patients who had hepatic mass, repeated transampullary at the time of re-stenting was positive for malignancy. Four of these 5 patients died 1, 2, 3 and 10 months during the follow-up; one patient was lost to follow-up. The other 2 transampullary biopsy negative patients who were not explored have remained in good condition for more than 2 years at the time of this report without clinical or laboratory evidence of malignancy. The results of transampullary biopsy-negative patients are summarized in Table 4. The causes of benign stricture were chronic pancreatitis in 3 patients and bile duct stricture post biliary surgery in 2 patients.

Statistically, endoscopic transampullary biopsy had sensitivity, specificity, positive predictive value and negative predictive value of 66.7 per cent, 100 per cent, 100 per cent and 31.3 per cent respectively.

Complications occurred in 15 of the 32 patients (46.8%). Complications included cholangitis (12 patients), pancreatitis (2 patients), and bleeding from sphincterotomy (1 patient). There were two deaths from sepsis and multiorgan failure. All complications were related to the underlying diseases and none was attributed to transampullary biopsy per se. The patient who bled had endobiliary prosthesis for biliary drainage.

DISCUSSION

Differentiating benign from malignant causes of biliary obstruction is essential for the patients' management and prognosis. In patients with benign biliary stricture, endoscopic balloon dilatation may be used instead of exploratory laparotomy. During the past decades, the yields of different endobiliary cytology techniques have been investigated. Sensitivity values ranged from 20 per cent to 80 per cent (average 38%) in several reports (12-16), depending on the technique, and method of calculation as well as the site of malignancy. Endoscopic retrograde brush cytology was the least invasive and is currently preferred to the other methods. Current research, aimed at reducing the rate of unsatisfactory samples or at evaluating the yields of cytometry and molecular biology techniques, was expected to lower the rate of false negative results(17,18). Unfortunately, the sensitivity of this technique remained low when strictures were caused by extrinsic tumors.

Compared to brush cytology, endobiliary biopsy or transampullary forceps biopsy have been studied. A few studies reported comparison of forceps biopsy and brush cytology, and it is still controversial as to whether the combined use of these two techniques is more advantageous. Comparative evaluations were in favor of forceps biopsy, (19), but Kurzawinsky(6) pointed out that although forceps biopsy is theoretically more suitable than cytology to sample malignancies that spread submucosally or outside the bile ducts, it is a second-line technique because it requires a preceding endoscopic sphincterotomy, and its safety has not yet been completely assessed.

Compared to surgical biopsy, the sensitivity of forceps biopsy (Table 3) was 66.7 per cent in this study, similar to the sensitivity reported by Aabakken(10) and Pugliese(20) but lower than other reports(21,22). These discrepancies may be attributed to differences in origin and pattern of growth of malignancy (i.e., mucosal or submucosal), depth of infiltration of the bile duct wall by extrinsic malignancy, type of forceps used, and number of samples taken(21). The specificity of forceps biopsy was excellent in this study (100%), as well as in most other published studies(10-12). A low negative predictive value (31.3%) suggested that patients with negative study need more vigorous investigations to exclude malignant disease.

In this study, complications included cholangitis (46.8%), mild pancreatitis (6.2%) and bleeding (6.2%). Notably, there was no biliary perforation in our study. Biliary perforation is a severe complication and some authors have against using forceps biopsy routinely(23). A large specimen obtained and repeated biopsy at the same site might have accounted for this complication(23). The use of stiff forceps might also have played a key role. Small-caliber and softer forceps may be safer, even though the sample size would be smaller which necessitates in increasing the number of samplings. In the initial phase of this study, after using the standard biopsy forceps it was found too stiff to pass through the ampulla and once it broke the duodenoscope elevator. Later the smaller and softer pediatric biopsy forceps were used.

One disadvantage of forceps biopsy is it requires sphincterotomy to facilitate insertion of the forceps. However, Sugiyama(22) succeeded in transpapillary biopsy without sphincterotomy in 45 of 52 patients (87%). In our study, one patient was not sphincterotomised to get biopsies. However, patients with alleged malignant biliary stricture frequently require drainage procedures such as insertion of biliary prosthesis. In this study, 11 of the 32 patients (34.4%) required biliary endoprosthesis, and sphincterotomy is an indispensable part of this procedure.

Therefore, we advocate the use of this less invasive, safe, and effective technique for diagnosing alleged malignant bile duct stricture.

ACKNOWLEDGMENTS

The authors wish to thank Assistant Professor Prawat Nithiyanun from the Pathology Department for reviewing the pathology and Professor Sucha Kurathong for reviewing the manuscript.

(Received for publication on April 27, 1999)

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การวินิจฉัยท่อน้ำดีตีบตันจากมะเร็งด้วยการตัดชิ้นเนื้อผ่านปลายท่อน้ำดีโดยการใช้กล้องส่องตรวจลำไส้

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ผู้ป่วยดีซ่านจากท่อน้ำดีตีบตันเป็นปัญหาที่พบบ่อย การวินิจฉัยมักอาศัยอาการทางคลินิก อัลตร้าซาวนด์ หรือเอ็กซเรย์คอมพิวเตอร์ และภาพรังสีท่อน้ำดี ซึ่งส่วนใหญ่ไม่มีผลการตรวจชิ้นเนื้อทางพยาธิยืนยัน ดังนั้นผู้ป่วยท่อน้ำดีตีบตันจากสาเหตุอื่นอาจถูกวินิจฉัยผิดว่าเป็นมะเร็งท่อน้ำดี ทำให้แผนการรักษาไม่ถูกต้อง

การเก็บชิ้นเนื้อเพื่อตรวจทางพยาธิสามารถทำได้ โดยการใส่สายตัดชิ้นเนื้อผ่านปลายท่อน้ำดีเข้าไปยังส่วนที่สันนิษฐานว่าเป็นมะเร็ง โดยใช้กล้องส่องตรวจลำไส้เล็กร่วมกับการฉายภาพรังสี (Endoscopic transampullary forceps biopsy under fluoroscopy) ผู้วิจัยได้ใช้เทคนิคนี้ทำการศึกษาผู้ป่วยจำนวน 32 ราย ตั้งแต่เดือนสิงหาคม 2540 ถึง กรกฎาคม 2541 ผลชิ้นเนื้อที่ได้จากเทคนิคนี้พบว่าเป็นมะเร็ง (ผลบวก) 16 ราย ผู้ป่วยกลุ่มนี้นำไปผ่าตัด 11 รายได้ผลตรวจชิ้นเนื้อยืนยันว่าเป็นมะเร็ง 8 ราย ไม่สามารถเก็บชิ้นเนื้อได้ 3 ราย ผู้ป่วยที่ไม่ได้ผ่าตัด 5 ราย เมื่อติดตามต่อมาพบว่าทั้งหมดเสียชีวิตภายใน 5 เดือนหลังได้รับการวินิจฉัย

ผู้ป่วย 16 รายที่ได้ผลลบจาก Endoscopic transampullary biopsy ได้รับการผ่าตัด 9 ราย เก็บชิ้นเนื้อตรวจจากการผ่าตัดได้ 6 ราย พบว่าเป็นมะเร็ง 4 ราย ไม่ยืนยันว่าเป็นมะเร็ง 2 ราย ซึ่ง 2 รายนี้เมื่อติดตามผู้ป่วยต่อมาพบว่ามีลักษณะทางคลินิกที่บ่งชี้ว่าเป็นมะเร็ง ส่วนอีก 3 รายไม่สามารถเก็บชิ้นเนื้อเพื่อตรวจทางพยาธิได้ อย่างไรก็ตามจากการเฝ้าติดตามผู้ป่วย 3 รายนี้นานประมาณ 8-22 เดือน ไม่พบหลักฐานทางคลินิกว่าเป็นมะเร็ง ผู้ป่วย 7 รายที่ไม่ได้รับการผ่าตัดมี 5 รายที่มีลักษณะทางคลินิกที่บ่งว่าเป็นมะเร็งและในจำนวนนี้ 4 รายเสียชีวิตภายใน 1, 2, 3 และ 10 เดือนหลังการวินิจฉัยตามลำดับ อีก 1 รายขาดการติดตาม ส่วนผู้ป่วยอีก 2 ราย เมื่อติดตามผู้ป่วยประมาณ 2 ปี ทั้งสองรายยังปกติ

เมื่อเปรียบเทียบผลการวินิจฉัยมะเร็งโดยเทคนิคนี้กับผลชิ้นเนื้อที่ได้จากการผ่าตัด พบว่าเทคนิคนี้สามารถให้การวินิจฉัยมะเร็งด้วยความไว (sensitivity) 66.6% ความจำเพาะ (specificity) 100% ค่า positive predictive value 100% และค่า negative predictive value 31.3% และไม่พบภาวะแทรกซ้อนรุนแรงจากการใช้เทคนิคดังกล่าว

การศึกษานี้แสดงว่า Endoscopic transampullary forceps biopsy เป็นวิธีที่มีประโยชน์และมีประสิทธิภาพในการวินิจฉัยภาวะท่อน้ำดีตีบตันจากมะเร็ง

คำสำคัญ : Endoscopic Transampullary Biopsy, Malignant Bile Duct Stricture, Diagnostic Value

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