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Original article

Factors affecting the yield of endoscopic transpapillary bile duct biopsy for the diagnosis of pancreatic head cancer

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ABSTRACT

Background: Transpapillary biliary biopsy (TBB) is a simple endoscopic technique that can be performed during an initial biliary drainage session. This procedure has the potential to reduce the load of another tissue sampling in cases of pancreatic head cancer (PHC) with biliary stricture. The aim of this study is to identify factors associated with a positive outcome using TBB for PHC.
Methods: In total, 130 cases that underwent TBB for investigation of distal biliary stricture were included [62 cases of PHC, 36 cases of distal biliary cancer (DBC), and 32 cases of benign biliary stricture (BBS)]. Factors affecting the diagnostic efficiency of TBB were determined using univariate and multivariate logistic analyses.
Results: Cancer tissue was obtained in 31 cases (50%) of PHC and 33 cases (91.7%) of DBC. Multivariable analysis showed that ≧10 mg/dl of serum bilirubin level (odds ratio [OR]: 5.58; 95% confidence interval [CI]: 1.29–28.20; $P = 0.021$) and ≧3 tissue samplings (OR: 3.59; 95% CI: 1.02–14.27, $P = 0.046$) were independent factors affecting cancer-positive rate in cases of PHC. In >90% of resected cases of PHC, cancer involved the left side of the biliary mucosa and the range of cancer invasion (≧2/3 of circumference of biliary mucosa) was also a significant factor ($P = 0.001$).
Conclusions: PHC showing high level of serum bilirubin (>10 mg/dl) and high circumferential proportion of bile duct invasion (>2/3 judging from MDCT) is a good indication for biliary biopsy. Targeting the left-side wall and ≧3 tissue samplings will lead to the higher sensitivity.

1. Introduction

Diagnosis of pancreatic cancer is sometimes difficult without histological evidence. A tissue diagnosis may be required when evidence from imaging studies does not warrant resection or when the evidence indicates an unresectable lesion for which palliative chemoradiotherapy is appropriate. Recent reports point to the utility of endoscopic ultrasound guided fine needle aspiration (EUS-FNA) biopsies, as it shows a fairly high sensitivity (80–95%) for pancreatic cancer [1–4]. In contrast, few reports have examined transpapillary biliary forceps biopsy for obtaining histological samples directly from the biliary stricture. Biliary biopsy [5,6] is a simple and safe technique that can be done with minimum physical invasion during endoscopic retrograde cholangiopancreatography (ERCP). Since patients with biliary strictures often require ERCP for relief of jaundice and cholangitis, performing biliary biopsy during the initial endoscopic biliary drainage (EBD) [7] is a sensible strategy. The sensitivity of this technique is satisfactory for biliary cancer (83–89%) [8,9], but inconsistent results are obtained for pancreatic cancer (33–50%) [8–12]. Accurate histological diagnosis at the initial EBD would allow earlier appropriate therapy and eliminate the need for additional invasive procedures for tissue sampling. At present, the efficacy of biliary forceps biopsy has not been evaluated on surgically resected cases, and therefore little is known about the factors that can influence the effectiveness of biliary biopsy. The aim of this study was to evaluate the factors associated with a positive diagnosis using transpapillary biliary biopsy (TBB) for pancreatic head cancer (PHC).

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Table 1
Clinicopathological findings of cases with pancreatic head cancer, distal biliary cancer, and benign pancreatic mass.

Clinical findings	PHC ($n = 62$)	DBC ($n = 36$)	BPM ($n = 32$)
Gender			
Female	35.5% (22)[a]	22.2% (8)	15.6% (5)[b]
Male	64.5% (40)	77.8% (28)	84.4% (27)
Age (years old) [range]	66 [42–84]	70 [48–82]	65 [38–83]
Jaundice[#]	69.4% (43)	80.6% (29)[c]	56.3% (18)[d]
Serum CEA (ng/ml)* [range]	3.4 [0.5–93.6]	2.7 [0.5–8]	2.6 [0.9–9.4]
Serum CA19-9 (U/ml)* [range]	245 [2.0–14,897][e]	147 [2.0–27,288][f]	22 [1.3–1076][g]
Whipple's operation	50.0% (31)	97.2% (35)	0% (0)
EBD tube placement[§]	95.2% (59)	97.2% (35)	62.5% (20)
EST	69.4% (43)[h]	58.3% (21)	37.5% (12)[i]
Median Number of tissue sampling [range]	2 [1–7]	2 [1–4]	2 [1–4]

a vs. b: $P = 0.04$, c vs. d: $P = 0.03$, e vs. g, f vs. g, and h vs. i: $P < 0.01$.
PHC, pancreatic head cancer; DBC, distal biliary cancer; BPM, benign pancreatic mass; MDCT, multidetector computed tomography; BD, bile duct; ERC, endoscopic retrograde cholangiography; EBD, endoscopic biliary drainage; EST, endoscopic sphincterotomy.
[#]Jaundice was judged as positive when serum total bilirubin was >3 mg/dl or endoscopic biliary drainage tube was placed by the referral hospital.
*When the endoscopic biliary drainage was placed by the referral hospital, data of serological examination was excluded from the analysis.
[§]In 6 of 59 cases with pancreatic head cancer and 12 of 35 cases with distal biliary cancer, the endoscopic biliary drainage was placed by the referral hospital.

2. Materials and methods

2.1. Patients

Between September 2003 and April 2011, TBB was attempted in 130 patients (95 males and 35 females; median age: 67 years; range: 38–84 years) with distal biliary strictures (Table 1). In all cases, multidetector computed tomography (MDCT) was performed prior to ERCP. The final diagnosis was made based on the image findings, histological evidence, and clinical courses, as follows: The 130 cases consisted of 62 cases of PHC, 36 cases of distal biliary cancer (DBC), and 32 cases of benign pancreatic mass (BPM). BPM included 29 cases of autoimmune pancreatitis (AIP) and 3 cases of alcoholic mass forming pancreatitis (MFP).

Clinical data included age, sex, serum total bilirubin, serum carcinoembryonic antigen (CEA), and serum carbohydrate antigen 19-9 (CA19-9)(Table 1). Serum total bilirubin, CEA, and CA19-9 were measured prior to ERCP in all cases. Jaundice was defined when serum total bilirubin level was ≧3 mg/dl or when the EBD tube was placed by the referral hospital. In 76 of 98 (77.6%) malignant cases performed for biliary biopsy, EBD was inserted at the initial ERCP in our hospital. In 18 cases (18.4%), EBD had been already placed by the referral hospital (Table 1).

2.2. Criteria for clinical diagnosis of pancreatobiliary cancer by MDCT

MDCT was performed at the first visit to our hospital. Four-phase contrast-enhanced dynamic CT scans [unenhanced, early arterial (20 s after intravenous administration of the contrast), late arterial (40 s), portal venous (70 s), and delay phase (120 s)] were performed with a 16-detector row scanner (Aquilion 64 scanner, Toshiba Medical System, Tochigi, Japan). All patients received 100 ml of nonionic contrast material intravenously at a rate of 4 ml/s.

The CT diagnosis was defined as follows: Pancreatic cancer was a hypo-attenuating pancreatic mass in arterial phase, with/without a dilation of the upstream main pancreatic duct (MPD), distal pancreatic atrophy [13–16], and left axis deviation of the lower bile duct. Information on the level of late-phase enhancement was helpful to differentiate this from a benign pancreatic mass [17]. Biliary cancer was diagnosed as a thickened bile duct wall with strong enhancement or hyper-attenuation during arterial or portal venous phase [18,19], without obvious left-side deviation, pancreatic mass or dilated MPD. In 66 resected cases, the accuracy of current CT criteria was determined by comparison with pathological diagnosis in the differentiation between PHC and DBC.

Table 2
Cancer-positive rate of bile duct biopsy for pancreatic head cancer, distal biliary cancer, and benign pancreatic mass.

BD biopsy	PHC ($n = 62$)	DBC ($n = 36$)	BPM ($n = 32$)
Cancer (+)	50% (31)[a]	91.7% (33)[b]	0% (0)[c]
Cancer (−)	50% (31)	8.3% (3)	100% (32)

a vs. b, a vs. c, and b vs. c: $P < 0.001$.
BD, bile duct; PHC, pancreatic head cancer; DBC, distal biliary cancer.

2.3. ERCP and forceps biopsy

All patients gave their written informed consent for ERCP and specimen collection from the biliary stricture. The ERCP procedure was conducted in the standard manner. To avoid post-EBD pancreatitis and to facilitate subsequent tissue sampling, a minimal level of endoscopic sphincterotomy (EST) was performed in the most malignant cases using a standard traction-type sphincterotome (Clevercut®, Tokyo, Olympus, Japan) [7]. By placing a guidewire into the bile duct as a landmark, misinsertion of the forceps into the pancreatic duct was avoided, especially when the contrast medium spilled out towards the duodenum due to EST. Bile duct tissue was obtained by using FB-39Q forceps (Diameter: 1.95 mm, Olympus, Tokyo, Japan) and FB-44U forceps (Diameter: 1.0 mm, Olympus, Tokyo, Japan). One to seven biopsy specimens were taken from the biliary stricture from each patient. As a rule, we usually perform two times of biopsy from the stenotic site. We added the number of tissue sampling when the taken biopsy tissue is small or inadequate. Biopsy tissues were placed in 10% formalin and used for histopathological analysis. After biopsy, an EBD tube was placed for biliary drainage.

The specimens were examined histologically by an experienced GI pathologist (K.S., listed as a co-author). Histological classifications were divided into: (A) normal epithelium, (B) atypical epithelium, (C) suspicious for malignancy, and (D) malignancy. Tissues that were histologically suspicious for malignancy or that showed malignancy were judged as cancer-positive; all others were judged as cancer-negative. The cancer-positive rate determined by biliary forceps biopsy was compared between pancreatic cancer and bile duct cancer (Table 2). Complications of ERCP were evaluated according to the criteria described by Cotton et al. [20].

2.4. Final diagnosis

Of the 130 patients analyzed in this study, final diagnosis was made with histological confirmation by surgical materials in 66 cases. The 32 cases of the remaining 64 non-surgical cases were diagnosed as malignant. In 23 of 32 (71.9%) non-surgical malignant cases, the histological evidence of malignancy was obtained by the either BD biopsy, EUS-FNAB, pancreatic duct biopsy or bile duct juice cytology. In the remaining 9 cases, diagnosis of malignancy was made based on the CT criteria described, coupled with a clinical course that indicated malignancy, such as clinical progression or death from current cancer. In total, 89 of 98 (90.8%) malignant cases revealed the histological evidence of malignancy. In benign cases,