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Sensitivity of alternative testing for pancreaticobiliary cancer: a 10-y review of the literature

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ABSTRACT

Background: Biliary strictures present a diagnostic challenge to differentiate benign disease from hepatopancreaticobiliary (HPB) malignancies. Endoscopic retrograde cholangiopancreatography cytology is commonly performed in these patients; however, its sensitivity for diagnosis of HPB malignancy is poor (41.6%). Many adjunctive tests have been investigated to improve the sensitivity of HPB biopsies. To determine the best tests available, however, we reviewed the literature and performed a comparative analysis of all recently investigated tests and their sensitivities.

Methods: A PubMed search identified articles published between 2003 and 2014, describing alternate methods for diagnosing HPB malignancies, reported sensitivity, final pathology, and had data available online. Meta-analysis was conducted for tests with multiple articles. Tests with the highest sensitivity and specificities were reported.

Results: A total of 77 studies were identified. Meta-analysis was performed on the sensitivity of EUS-FNA (74.2%), fluorescence *in situ* hybridization (54.2%), immunostain of insulin-like growth factor 2 mRNA-binding Protein 3 (IMP3; 80.4%), IMP3 + cytology (86.4%), K homology domain containing protein overexpressed in cancer (KOC; 85.9%), S100P (77.8%), serum CA19-9 (69.3%), and K-ras mutations (47.0%) to detect malignancy. Ultimately, 12 tests were identified with superior sensitivity (85.3%–100%) and specificities (81.6%–100%) including stricture scrapping, brush sectioning, IMP3 stain + cytology, IMP3+S100A4, bile carcinoembryonic cell adhesion molecule 6 protein (±CA19-9), bile micro RNA (miRNA)-135b, serum miRNA-RNU2-1f, serum miRNA-21 (+CA19-9), peripheral blood mononuclear cells miRNA-27a-3p (+CA19-9), serum miRNA-16 + miRNA-196a (+CA19-9), peripheral blood mononuclear cells mRNAs h-TERT + CK20 + CEA + C-MET.

Conclusions: We recommend immunostaining with a panel of IMP3+KOC + S100A4 + cytology to achieve maximum sensitivity and specificity from HPB biopsies. One biliary protein

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(carcinoembryonic cell adhesion molecule 6) and several RNAs (bile and blood) offer exceptional sensitivity and specificity and should be tested prospectively in larger populations. Overall, this review identifies several tests to improve the sensitivity of diagnostic algorithms to identify HPB malignancies.

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1. Introduction

Pancreatic and biliary tract malignancies, both intra- and extra-hepatic, represent major morbidity and mortality in the United States with an estimated combined incidence of more than 57,000 associated with more than 42,400 estimated deaths yearly [1–5]. These malignancies typically present as biliary strictures, sometimes without obvious tumor on radiographic imaging [6–8]. However, several benign conditions can also present with biliary strictures such as chronic pancreatitis, primary sclerosing cholangitis, choledocholithiasis, and postoperative strictures. As a result, these malignancies represent an especially difficult diagnostic and therapeutic challenge to clinicians as the management of benign biliary strictures differs drastically from malignant biliary strictures, which typically require surgical intervention. The pancreaticoduodenectomy (Whipple) and liver resections are the surgical management for malignancies in the head of the pancreas or for intrahepatic cholangiocarcinomas, respectively. These carry a perioperative mortality of 1.6%–4.9% [9,10], and morbidities ranging between 20% and 60% [11–18]. More importantly, patients who undergo Whipple procedures for benign diagnosis experience a 17% drop in long-term survival at 10 y [19]. Accurate preoperative diagnosis is therefore critical in identifying those patients that can safely avoid the morbidity and mortality of a large operation. In practice, however, this diagnostic goal has been difficult to achieve. The typical workup of biliary stricture involves endoscopic retrograde cholangiopancreatography (ERCP), bile duct brushings, and cytologic analysis. This diagnostic approach has been applied to both distal and proximal (intrahepatic) biliary strictures although percutaneous transhepatic cholangiography can be used to obtain brushings for more proximal strictures [20–23]. Pathologic analysis of bile duct brushings has been plagued with low sensitivity, and historically wide variability (30%–88%) has been found in these reports [24,25]. To address this problem, a recent meta-analysis by this group established the precise sensitivity of ERCP cytology to be 41.6 ± 3.2% (99% confidence interval [CI]) and a negative predictive value of 58.0 ± 3.2% (99% CI) [26]. Endoscopic ultrasound-guided fine needle aspiration biopsy (EUS-FNA) can also be used to obtain tissue diagnosis; however, this modality is also plagued by low sensitivity [27]. As a result, some patients even undergo a major resection without a preoperative tissue diagnosis.

A significant amount of investigations have focused on creating adjunctive tests to improve diagnostic sensitivity of hepatopancreaticobiliary (HPB) biopsies. These have ranged from tumor markers [28–30], immunohistochemistry [31], mutational analysis [32,33], DNA ploidy analysis [34,35], and fluorescence *in situ* hybridization (FISH) [36,37]. These efforts have met with limited success and therefore limited to no impact on the clinical standard of care. Nevertheless, several of these modalities show promise in improving the accuracy of current diagnostic algorithms. Therefore, we have undertaken a comprehensive review and comparison of all alternate modalities that have been attempted over the last 10 y to improve the sensitivity of detecting HPB malignancies in high-risk patients. Multiple studies were identified examining the sensitivity of the same test in similar patient populations, and these were compiled into meta-analysis. This study aims to identify the most promising candidate biomarkers for improving the current clinical approach to diagnosis of HPB malignancies.

2. Methods

2.1. Literature search

The following search terms were used in separate PubMed searches: (1) "ERCP sensitivity," (2) "ERCP FISH sensitivity," (3) "(biliary OR pancreatic) and cancer and polymerase chain reaction and sensitivity," and (4) "(pancreatic or biliary) and cancer insulin-like growth factor 2 mRNA-binding protein 3." This strategy yielded a combined total of 1821 articles, 987 of which were published between 2003 and 2014. An additional search strategy "EUS-FNA and sensitivity and (biliary OR pancreatic) and cancer" was used to identify articles for EUS-FNA sensitivity meta-analysis. Inclusion criteria were (1) English language, (2) study population composed of patients with biliary stricture, (3) ERCP brushing cytology results available, (4) study population with final diagnosis available either by surgical pathology or disease progression on long-term follow-up, and (5) that the study data were available online. Exclusion criteria included (1) study population already included in another study, (2) review articles, and (3) insufficient data to calculate sensitivity. Ultimately, 77 studies and 82 tests and test panels were identified and are listed in Tables 1–10. In some cases, study populations had to be limited to include only those patients who had a histopathologic diagnosis. If multiple arms of a study were available, the study arm comparing all HPB malignancies to all normal and benign disease was selected for inclusion. If cytology results were included, only truly malignant cytology was considered as positive.

2.2. Statistical analysis

Each study was analyzed for total number of individuals in the study (*N*), the true positive (pathology positive results or path+), and the test positive (number of patients with positive test results who have disease or test+). The sensitivity and 95% CI were then calculated. In some cases, studies provided the sensitivity (based on the receiver operator curve and cutoff value), and the test+ was calculated based on the number of path plus patients. In each meta-analysis data set, the studies were treated as one large retrospective group. The *N*, path+,

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