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Invited Review Article

Management of malignant distal biliary obstruction

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A B S T R A C T

The most common cause of malignant distal biliary obstruction is pancreatic cancer, as 70–90% of patients will develop jaundice during the course of their disease. Pancreatic cancer is usually advanced at presentation, and curative resection is possible in < 15% of patients. If a patient is to undergo early surgical resection, biliary drainage is not prerequisite. Early surgery without preoperative biliary drainage does not increase the risk of complications, as compared with preoperative biliary drainage, followed by surgery. Postoperative complications do not differ significantly between the two approaches. In light of no significant improvements in patient survival in large trials of a surgery-first followed by adjuvant therapy over the past 2 decades, there has been a shift towards preoperative neoadjuvant chemotherapy in the setting of borderline resectable disease. Consequently, effective preoperative biliary drainage has become a paramount concern in this setting. Multiple retrospective and prospective studies have compared the outcomes between covered metal stents and uncovered metal stents in malignant biliary obstruction. In patients undergoing neoadjuvant chemoradiation or surgical resection, no significant self-expanding metal stent-related complications or adverse events were seen. Additionally, no significant difference in overall survival was seen between the two groups. Within the palliative realm, self-expanding metal stents have also become the stent of choice with greater duration of patency. In an effort to deliver a survival benefit, there are many ongoing trials and developments in the realm of the therapeutic endoscopy. In this review, we will examine what we have accomplished and further explore the potential benefits of endoscopic interventions on the horizon.

Keywords: biliary brushings, cholangiocarcinoma, endoscopic retrograde cholangiopancreatography, pancreatic cancer, self-expanding metal stent

Introduction

Malignant biliary strictures most commonly arise from either pancreatic cancer or cholangiocarcinoma. Often the first presentation of these cancers is with jaundice and biliary obstruction. Unfortunately most of these also present in the late stages of the disease. The most recent Surveillance, Epidemiology, and End Results data show the overall 5-year survival rate of pancreatic cancer at 6–7%. If detected early with only local disease (reported as approximately 10% of cases), the survival rates are better but still abysmal at approximately 25%.[1] Similarly, the 5-year survival with extrahepatic biliary cancer after resection was approximately 30% but 0% in those cases that were unresectable.[2] Given these sobering statistics, the goal with early stage disease is to proceed to therapy in an efficient and timely manner, specifically to get to surgical resection, as this is the only hope for cure. Palliative therapy by contrast focuses on relief of symptoms and delay of disease progression.

This review discusses the rationale for screening high risk patients, the diagnosis of malignant strictures, the endoscopic therapy currently available for these strictures, and possible future therapies in the pipeline.

Screening

Approximately 10–20% of pancreatic cancers may have an underlying genetic predisposition.[3,4] Although screening would not be appropriate for the general population, consideration of screening in high-risk individuals may be useful if a highly sensitive and cost-effective test is identified. Groups with known genetic syndromes that predispose them to an increased risk of pancreatic cancer are most likely to benefit from screening. The highest risk patients include those with Peutz–Jeghers syndrome (STK11/ LKB1 mutation), familial atypical multiple mole melanoma (p16/CDKN2A mutation), Lynch syndrome (MLH1, MSH2, MSH6, and PMS2 mutations), hereditary breast and ovarian cancer syndrome (BRCA1/2 mutations), and hereditary pancreatitis (PRSS1 mutation). Additionally those with a strong family history of pancreatic cancer (familial pancreatic cancer) may also be appropriate for screening. Those patients with three or more first-degree relatives are at a 32-fold increased lifetime risk of pancreatic cancer. Mutations in PALB2 have been associated with familial pancreatic cancer.[3]

Multiple studies have assessed imaging modalities for screening of pancreatic cancer.[3,5] A large study across five United States institutions compared computed tomography (CT), magnetic reso-

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nance imaging (MRI), and endoscopic ultrasound (EUS) in 225 asymptomatic high-risk adults and showed that EUS was the best modality to detect a pancreatic abnormality (11%, 33.3%, and 42.6% respectively).[6] Currently there are no specific guidelines as to how to screen and what age to start this process, but EUS or MRI seems to be the best currently available modality for early detection in these high risk patients.

Development of new technology for better screening for pancreatic cancer is needed. Evaluation of optical markers in the periampullary duodenum with low-coherence enhanced backscattering has been reported to discriminate between healthy controls and patients with pancreatic adenocarcinoma with 95% sensitivity, 71% specificity, and 85% area under the receiver operator characteristic curve. Additionally these numbers were not affected when looking specifically at resectable stage disease.[7] Further study is underway to better elucidate the utility of this technology and assess whether it may be a promising technique for screening.

Diagnosis

Distinguishing between malignant and benign strictures in an efficient manner may portend a better chance for cure for local disease but also for those patients with borderline resectable disease. Imaging studies as well as stricture sampling provide complementary information regarding both the etiology of the stricture but also the extent of disease.

Multiple imaging modalities have been studied to assess the best method of detection and differentiation between malignant and benign strictures.

A prospective study assessing magnetic resonance cholangiopancreatography (MRCP) compared to CT, endoscopic retrograde cholangiopancreatography (ERCP), and percutaneous transhepatic cholangiography for the diagnosis of malignant biliary strictures versus benign strictures showed comparable sensitivities and specificities for ERCP versus MRCP (sensitivity 85% for both and specificity of 75% for ERCP and 71% for MRCP). CT had lower sensitivity and specificity compared to both ERCP and MRCP.[8] Although MRCP was comparable, ERCP provides the ability to sample the stricture as discussed below, which may make it a more attractive study despite the invasiveness of the test.

The sensitivity and specificity of fludeoxyglucose-positron emission tomography (^{18}FDG-PET) to distinguish malignant from benign strictures has varied widely across studies and for different anatomic locations (intrahepatic versus perihilar versus extrahepatic). In one study of 93 patients with cholangiocarcinoma undergoing preoperative ^{18}FDG-PET scans, the sensitivity and specificity for intrahepatic versus extrahepatic lesions was 95% and 100% versus 69.2% and 66.7% respectively.[9] An additional study comparing ^{18}FDG-PET with conventional imaging modalities (CT and MRI) showed no statistically significant advantage in favor of ^{18}FDG-PET for diagnosis but did show higher accuracy over CT in the diagnosis of regional and distant metastases, suggesting that ^{18}FDG-PET should be an adjunct to other modalities for staging purposes.[10] The use of ^{18}FDG-PET for not only diagnosis but also staging and follow-up for cholangiocarcinoma has been reviewed separately beyond the details above.[11]

Studies on the yield of biliary brushings during ERCP have shown a wide range of sensitivities from approximately 30% to 60%.[12] Performing multiple brushings has been shown to increase sensitivity, and after three consecutive negative brushings, the probably of malignancy is very low.[13] Sensitivity does not seem to increase with dilation.[14] Improvement in sensitivities with some of these methods is thought to be related to disruption of the biliary epithelium, yielding better access to malignant cells.

Studies of results with endobiliary forceps biopsies have shown increased sensitivities, on average around 60%, but this method is time consuming and technically difficult and therefore not used on a routine basis.[12]

In a prospective comparison of ERCP with biopsies or brushings and EUS-guided fine needle aspiration (FNA) in patients with both biliary and pancreatic pathology, ERCP-based techniques were superior for the subgroup with biliary tumors (ERCP 75% vs. EUS 25%), and EUS-FNA guided biopsy was better in the subgroup with pancreatic masses (EUS 60% vs. ERCP 38%).[15] A more recent study published in *Gastrointestinal Endoscopy* in July 2014 compared EUS-guided FNA to ERCP tissue sampling with brushings and forceps biopsy. This was a prospective, single-blinded trial of same session EUS and ERCP for malignant biliary strictures. The overall sensitivity and accuracy was 94% and 94% respectively for EUS compared to 50% and 53% for ERCP sampling. This study also confirmed comparable sensitivity for biliary masses but superior sensitivity for EUS-FNA over ERCP in strictures related to pancreatic masses.[16]

FNA needle size has been investigated to determine sample adequacy. A meta-analysis of 22-gauge needles versus 25-gauge needles for FNA of solid pancreatic masses showed that 25-gauge needles were more sensitive than 22-gauge needles for the diagnosis of malignancy (93% versus 85%).[17] In another study, the 25-gauge needles were again superior over 22-gauge but also over 19-gauge Trucut core biopsy needles as well.[18] Additional core biopsy needles have been developed as well. A 22-gauge core needle in one small study did not show superior diagnostic results over the 22-gauge FNA needle.[19] Most recently a 25-gauge core biopsy needle was studied and produced high sensitivities on each of three passes (83%, 91%, and 96%) despite low histological core biopsy yields (32%).[20] Randomized studies comparing the 25-gauge core needles and standard FNA needles are needed.

Finally, the combination of sampling methods appears to increase the yield of diagnosis. A study of 133 patients undergoing ERCP for jaundice underwent trimodal tissue sampling by brushing, endobiliary forceps biopsy, and fine-needle aspiration cytology. 104 patients had a malignant stricture with (46 pancreatic, 30 cholangiocarcinoma, 13 ampullary, and 15 metastatic). The highest yield of sampling regardless of type was seen with ampullary cancers. The combination of techniques was superior to any one alone.[21]

Despite the investigation of numerous adjunctive tests to routine cytology and histology, only fluorescence *in-situ* hybridization (FISH) has seen consistently optimistic results. This technique uses fluorescently labeled DNA probes to assess for polysomy on certain predetermined chromosomal loci. In a study by Fritcher et al,[22] 498 brushings from pancreaticobiliary strictures were assessed with FISH versus routine cytology. The sensitivity of polysomy FISH was 42.9%, which was significantly higher than routine cytology (20.1%). Specificity approached 100% for both.[22] Additional studies have confirmed this result and in fact exceeded the sensitivity value.[23–25] Given these findings, the use of FISH in the setting of negative or indeterminate routine cytology has been recommended in recent guidelines by The Papanicolaou Society of Cytopathology.[26]

Endoscopic therapy

Stenting

Previously it was thought that preoperative drainage was beneficial as, theoretically, drainage was thought to decrease complications related to cholestasis including cholangitis, impaired clotting and immunological response, and fat malabsorption. Despite lack of evidence for it,[27] preoperative drainage has been