

Pancreatic Cancer:

The Role of Endoscopic Ultrasound



Jennifer A. Flemming, MD; and Lawrence C. Hookey, MD, FRCPC

Presented at Queen's University Mini Med School for the Public, Kingston, Ontario.

Pancreatic cancer is the eleventh most common malignancy in Canada but is the sixth leading cause of cancer death with 3,500 people receiving the diagnosis and 3,400 patients succumbing to the disease in 2006.¹ Unfortunately, only 20% of patients at presentation are candidates for surgical cure and of those, only 25% to 30% of them are alive at five years.

Patients who gain the most benefit from curative surgery are those who have no evidence of lymph node involvement or lymphovascular invasion. Therefore, accurate staging of patients with pancreatic cancer is critical to avoid the expense, morbidity and mortality related to unnecessary surgery.

Approach to the patient with painless jaundice

A history and physical examination can usually provide important clues as to the etiology of a patient presenting with jaundice. Key points to cover are:

- Medication use
- Alcohol consumption
- Travel history
- Injection drug and cocaine use
- Blood transfusions
- History of incarceration
- Tattoos
- Sexual history

Mary's case

Mary, 59, presents to her FP with a 3 week history of painless jaundice. She is also experiencing debilitating back pain, pruritis and weight loss.

Investigations

An abdominal ultrasound does not show any evidence of gallstones but does show intrahepatic and common bile duct dilation.

A CT scan of the abdomen demonstrates a mass in the head of the pancreas abutting the superior mesenteric vein, thought to be unresectable (Figure 1).

An endoscopic retrograde cholangiopancreatography (ERCP) shows a biliary stricture which is stented successfully (Figure 2). Pathology from endoscopic brushings do not reveal a diagnosis.

Diagnosis

A biopsy is obtained using endoscopic ultrasound (EUS) confirming the diagnosis of adenocarcinoma (Figure 3). EUS is also able to show that there is no lymphovascular invasion of the tumour into surrounding structures and no involved lymph nodes.

Treatment

During the EUS, a celiac plexus block is performed to help alleviate Mary's back pain.

Based on the findings of the EUS, Mary goes on to have a curative Whipple's procedure for the pancreatic adenocarcinoma.



Figure 1. A CT scan of the abdomen showing the proximity of the pancreatic mass to the superior mesenteric vein (arrow).



Figure 2. ERCP showing common bile duct and intrahepatic duct dilation with an absence of contrast dye at the level of the biliary obstruction (arrow).

- Immunization for Hepatitis A/B
- Family history

Jaundice coupled with a palpable, non-tender gallbladder (Courvoisier's sign) is suggestive of a pancreatic head mass, while fatigue, anorexia, malaise and myalgias may imply a viral hepatitis.

Obstructive jaundice is classically associated with pale stools and dark urine. Pruritis is also an important symptom to elicit during the initial assessment as it is present in 50% of patients presenting with primary biliary cirrhosis (PBC) and can be an indication for certain therapeutic interventions. Stigmata of chronic liver disease should be evaluated during physical examination (Table 1).

Differential diagnosis and initial evaluation of painless jaundice

Painless jaundice associated with conjugated hyperbilirubinemia can be a result of either intrahepatic or extrahepatic cholestasis (Table 2). Initial evaluation should include:

- complete blood count,

- electrolytes,
- creatinine,
- urea,
- liver enzymes,
- alkaline phosphatase,
- albumin,
- INR and
- total/direct and indirect bilirubin.

An elevated bilirubin with a predominant elevation in the liver aspartate and alanine transaminases are suggestive of an intrahepatic cause, while an elevated bilirubin with a predominant elevation in alkaline phosphatase is suggestive of an obstructive process.

If an intrahepatic or extrahepatic cause cannot be differentiated from the laboratory evaluations, then imaging is the next investigation.

Abdominal ultrasound

Abdominal ultrasound (U/S) is usually the initial modality ordered because of the wide availability and relatively low cost. The sensitivity of detecting dilated bile ducts or bile duct obstruction ranges from 55% to 91%.² CT scans are equally as effective as an U/S at detecting

hepatic duct dilation² but less sensitive at detecting cholelithiasis since a CT evaluation of non-calcified stones is poor.

Differential diagnosis of a pancreatic head mass

The differential diagnosis of a pancreatic head mass is listed in Table 3. The sensitivity and specificity for a pancreatic head mass on U/S is 75% to 89% and 90% to 99%³ respectively, while an abdominal CT evaluation is 85% to 90% sensitive and 90% to 95% specific.⁴ A CT scan also has the advantage of being able to assess lymphadenopathy, detect hepatic lesions and can evaluate vascular invasion using contrast dye.

Why do patients with jaundice experience pruritis?

Pruritis is a common feature of both intra- and extrahepatic biliary obstruction. Historically, it has been taught that the deposition of bile salts in the skin causes the sensation of pruritis as supported by studies showing bile salt deposition in skin biopsies and the ability of administered bile acids to induce pruritis. However, this theory is falling out of favour based on more recent evidence documenting the cessation of pruritis despite ongoing cholestasis, the absence of pruritis in patients with elevated levels of bile acids and the lack of correlation between the severity of pruritis and the concentration of bile acid in the plasma.⁵

Most recently, endogenous opioids have been implicated as the pathophysiologic factor in cholestatic pruritis. The sensation of pruritis is transmitted through slow-conducting nociceptive neurons with free nerve endings in the dermoepidermal junction which are activated

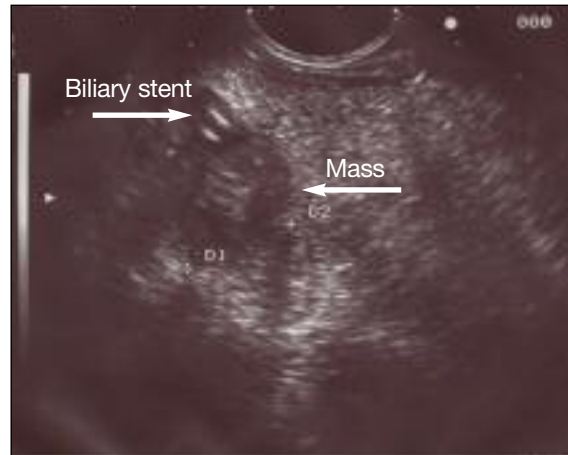


Figure 3. Endoscopic ultrasound image demonstrating pancreatic mass adjacent to a stented common bile duct.

Table 1

Stigmata of chronic liver disease

- Palmar erythema
- Terry's nails
- Spider nevi
- Scleral icterus
- Gynecomastia
- Splenomegaly
- Clubbing
- Bruising
- Fetor hepaticus
- Asterixes
- Ascites
- Hypogonadism

In 2006, 3,400 patients succumbed to pancreatic cancer.

Dr. Flemming is a PGY-2, Department of Internal Medicine, Queen's University, Kingston, Ontario.

Dr. Hookey is an Assistant Professor, Division of Gastroenterology, Department of Medicine, Queen's University, Kingston, Ontario.

Table 2

Differential diagnosis of intrahepatic and extrahepatic cholestasis

Intrahepatic cholestasis	Extrahepatic cholestasis
<ul style="list-style-type: none"> • Viral hepatitis • Alcoholic hepatitis • Nonalcoholic steatohepatitis • Primary biliary cirrhosis • Drugs and toxins • Sepsis and hypoperfusion • Infiltrative diseases • Fatty liver of pregnancy 	<ul style="list-style-type: none"> • Choledocolithiasis • Intrinsic tumours (<i>i.e.</i>, cholangiocarcinoma) • Extrinsic tumours (<i>i.e.</i>, pancreatic cancer, lymph nodes) • Primary sclerosing cholangitis • Acute/chronic pancreatitis • Pseudocysts • Strictures

by histamine, substance-P, serotonin and opioids. Patients with liver disease have, through unknown mechanisms, elevated levels of endogenous opioids. Several studies have now shown a reduction in cholestatic pruritis with the administration of opioid antagonists.^{6,7}

For patients with pruritis related to intrahepatic cholestasis, the treatment of choice is the correction of the underlying disorder. If this is not possible, cholestyramine may be used at 4 g to 16 g q.d. in divided doses. Other options include rifampin, methotrexate, colchicine, nalaxone, phenobarbitol and liver transplantation. For those with extrahepatic cholestasis, relief of the obstruction or drainage are the treatment options.

A CT scan also has the advantage of being able to assess lymphadenopathy, detect hepatic lesions and can evaluate vascular invasion using contrast dye.

Endoscopic ultrasound (EUS) in the diagnosis, staging and treatment of pancreatic cancer

EUS is a small ultrasound probe mounted in the tip of an endoscope which allows ultrasonography to visualize structures of the digestive tract and surrounding tissues and organs. EUS has recently become a valuable modality in the diagnosis and staging of pancreatic cancer. Large studies have shown the tumour (T) staging accuracy of EUS to be between 78% and 94% and the nodal status (N) staging between 64% and 82%. It also has the ability to provide fine needle aspiration of any suspicious lesions.

Multiple studies have compared helical CT scan to EUS in staging pancreatic cancer. A review article including four studies and 164 patients concluded that compared to helical CT, EUS detected significantly more tumours (94% vs. 73%), was more accurate at determining respectability (91% vs. 83%) and was more sensitive at detecting vascular invasion (91% vs. 34%).⁸

In addition to the staging of pancreatic cancer, EUS can also be of therapeutic value. Pain related to pancreatic cancer can be debilitating. Although usually responsive to narcotic

Table 3


Differential diagnosis of pancreatic head mass

• Pancreatic exocrine neoplasm	• von Hippel-Lindau syndrome
• Papillary pancreatic neoplasm	• Neurofibroma
• Pancreatic pseudocyst	• Duodenal diverticula
• Pseudoaneurysm	• Pancreatic sarcoma
• Benign pancreatic cyst	• Pancreatic lymphoma
• Serous cystadenoma	• Abscess
• Traumatic hematoma	• Metastatic tumour

Take-home message

- Painless jaundice has a broad differential diagnosis that can be narrowed down by history, physical exam, bloodwork and imaging
- Pancreatic cancer is almost universally fatal unless patients present to medical attention while it is still potentially curable by surgical resection
- EUS is a valuable tool in the diagnosis and staging of pancreatic cancer and also has therapeutic value in the ability to provide pain relief by celiac plexus neurolysis

analgesic, the associated side-effects of constipation, nausea and delirium can limit the dosage used by patients. Celiac plexus neurolysis (CPN) is a chemical splanchnicectomy that obliterates the afferent nerve fibres that transmit pain to the intrabdominal viscera and can be preformed during EUS. Several small studies have evaluated the efficacy of CPN by EUS for pain related to pancreatic cancer. A pilot study of 25 patients found that 88% received a median of 10 weeks of pain relief after CPN.⁹ Another prospective study of 58 patients showed that 78% had significantly lower pain

scores two weeks after the procedure and this lasted for a median of 24 weeks.¹⁰ Timing of the procedure has also been found to predict the degree of response to CPN with patients receiving CPN early in the course of the disease having better pain relief. 

References

1. Canadian Cancer Society. www.cancer.ca. Accessed Jan 28, 2008.
2. Pasanen PA, Partanen KP, Pikkarainen PH, et al: A Comparison of Ultrasound, Computed Tomography and Endoscopic Retrograde Cholangiopancreatography in the Differential Diagnosis of Benign and Malignant Jaundice and Cholestasis. *Eur J Surg* 1993; 159(1):23-9.
3. Maringhini A, Ciambra M, Raimondo M, et al: Clinical Presentation and Ultrasonography in the Diagnosis of Pancreatic Cancer. *Pancreas* 1993; 8(2):146-50.
4. Pasanen PA, Eskelinen M, Partanen K, et al: A Prospective Study of the Value of Imaging, Serum Markers and their Combination in the Diagnosis of Pancreatic Carcinoma in Symptomatic Patients. *Anticancer Res* 1992; 12(6B):2309-14.
5. Ghent CN, Bloomer JR, Klatskin G, et al: Elevations in Skin Tissue Levels of Bile Acids in Human Cholestasis: Relation to Serum Levels and Toppruritus. *Gastroenterology* 1977; 73(5):1125-30.
6. Bergasa NV, Alling DW, Talbot TL, et al: Effects of Naloxone Infusions in Patients with the Pruritus of Cholestasis. A Double-Blind, Randomized, Controlled Trial. *Ann Intern Med* 1995; 123(3):161-7.
7. Wolfhagen FH, Sternieri E, Hop WC, et al: Oral Naltrexone Treatment for Cholestatic Pruritus: A Double-Blind, Placebo-Controlled Study. *Gastroenterology* 1997; 113(4):1264-9.
8. Hunt GC, Faigel DO: Assessment of EUS for Diagnosing, Staging and Determining Resectability of Pancreatic Cancer: A Review. *Gastrointest Endosc* 2002; 55(2):232-7.
9. Wiersema MJ, Wiersema LM: Endosonography-Guided Celiac Plexus Neurolysis. *Gastrointest Endosc* 1996; 44(6):656-62.
10. Gunaratnam NT, Sarma AV, Norton ID, et al: A Prospective Study of EUS-Guided Celiac Plexus Neurolysis for Pancreatic Cancer Pain. *Gastrointest Endosc* 2001; 54(3):316-24.



EZETROL® is indicated as adjunctive therapy to diet, when the response to diet and other non-pharmacological measures has been inadequate.

EZETROL®, administered alone or with a statin, is indicated for the reduction of elevated TC, LDL-C, Apo B, and TG and to increase HDL-C in patients with primary hypercholesterolemia.

EZETROL®
ezetimibe

CHOLESTEROL ABSORPTION INHIBITOR

PRODUCT MONOGRAPH AVAILABLE UPON REQUEST

®Registered trademark used under license by Merck Frosst-Schering Pharma, G.P.

MERCK FROSST / Schering
Pharmaceuticals
Merck Frosst-Schering Pharma, G.P.
Kirkland, Quebec H9H 3L1

PAAB

EZT-06-CDN-44200537F-JA