Does Endoscopic Ultrasound (Eus) Guided Fine-Needle Aspiration (Fna) Of Lymph Nodes During The Preoperative Staging Of Pancreatic Cancer Increase Post-Operative Survival?

David Milkes

A. Background

Pancreatic cancer affects approximately 27,000 new patients a year. It is the fourth leading cause of cancer death amongst men, and the fifth amongst women.[1] At the time of diagnosis, 90% of patients present with late-stage disease which is currently incurable. However, a portion of the 10% of patients with local disease is surgically curable with 5 year survival rates between 14%-33%[2]. Why aren't more patients with local disease cured?

Approximately 5% of the mortality is directly related to the surgery.[3] The majority of mortality is likely due to the inability to detect metastatic disease. Therefore, accurate preoperative staging is important to determine which patients may benefit from surgical resection and to avoid unnecessary surgery in patients deemed to be incurable Several modalities are currently available to assess preoperative staging including CT, US, angiography, EUS, and laparoscopy. EUS combined with other modalities has been shown effective for staging pancreatic cancer.[4] Whereas EUS has been praised for its sensitivity in T staging (80-90%), it has been criticized for its lower sensitivity in N staging (60%). This limitation of EUS is due to its inability to differentiate between malignant and inflammatory lymph nodes.[5] The advent of EUS FNA may enable more accurate preoperative staging of pancreatic neoplasms thereby improving the selection of surgically resectable patients.

EUS guided fine needle aspiration is generally regarded as safe and accurate, especially when using a curved linear array echoendoscope. A recent study of 44 patients suspected of having pancreatic cancer who underwent EUS FNA staging reported that 12 of 44 (27%) patients avoided surgery.[6] In that study, EUS FNA of lymph nodes increased the number of patients who could avoid surgery by 30%. Selecting out patients deemed incurable by surgery is beneficial because it reduces costs, and protects patients from a high morbidity, high mortality procedure. It would also enable these patients to more quickly enroll in protocols studying alternative treatments. Additionally, given the high sensitivity (95%) and specificity (95-100%) of EUS FNA lymph node biopsy[7], it is likely that patients with biopsy proven negative nodes are truly node negative and will therefore have higher surgical cure rates.

B. Hypothesis

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[1] Schwartz, et. al. Principles of Surgery. 6th edition. McGraw-Hill, Inc.: New York, 1994, pp. 1421 -1424.

[2] Wanebo, HJ. "Pancreatic Cancer in Perspective. A Continuing Challenge." Cancer. 78 (3 Suppl) 580-591, 1996 August 1

[3] Wanebo, HJ. Ibid.

[4] Gress, FG, et. al. "Endoscopic ultrasound- guided fine-needle aspiration biopsy using linear array and radialscanning endosonography." Gastrointestinal Endoscopy. 45 (3) 243-250, 1997 August.

[5] Chang, KJ, et. al. "The clinical utility of endoscopic ultrasound- guided fme-needle aspiration in the diagnosis and staging of pancreatic carcinoma." Gastrointestinal Endoscopy. 45 (5) 387-393, 1997 May 90

[6] Chang, KJ, et. al. Ibid.

[7] Stotland, BR. et. al. "Diagnostic and therapeutic endosonography: endoscopic ultrasound guided fineneedle aspiration in clinical practice." Gastrointestinal Endoscopy. 45 (3) 329-331, 1997 March

EUS FNA of lymph nodes during the preoperative staging of pancreatic cancer increases post-operative survival.

C. Study design

This will be a randomized prospective study of consecutive patients suspected of having pancreatic cancer who are undergoing staging EUS at Columbia-Presbyterian Hospital. Patients referred from outside institutions will be included. Patients who qualify for enrollment and sign the appropriate consent will proceed with EUS staging to confirm eligibility. Patients staged as operable will be randomly assigned either to FNA of lymph nodes or no FNA of lymph nodes. All biopsy negative and non-biopsied patients will proceed to surgery either at CPMC or their referral institution. Node positive patients will be disqualified from the study, and will be instructed to discuss treatment options with -their primary physician. Post-operatively, all patients will be followed up at CPMC every 3 months for the first 2 years, and then every 6 months for the next 3 years to assess mortality. Alternatively, communications directly with the patient or their referring physician can be done at the above end-points to assess mortality. Kaplan Meyer survival curves will be used to compare mortality in the two groups.

Using an alpha of 0.05 and beta of 80%, in order to detect a 50% mortality rate in the "biopsy group" vs. a predicted mortality of 75% in the "control no biopsy group", 60 patients will be needed in each group.

D. Subiects

a. Inclusion Criteria:

- Only patients diagnosed or suspected of having pancreatic adenocarcinoma isolated to the head of the pancreas will be eligible because tumor in the body and tail is rarely curable. Patients with high clinical suspicion of pancreatic cancer (symptoms of jaundice, weight loss, abdominal pain, new onset diabetes) who have been ruled for other causes of obstructive jaundice (i.e. choledocholithiasis, ampullary tumors, duodenal cancer) and have no evidence of metastatic disease on CT may be enrolled. Also, any patient diagnosed by CT guided biopsy or EUS FNA of the pancreas and no evidence of metastasis may participate. Patients must be good surgical candidates. Patients must be over the age of 18. Patients with chronic pancreatitis may be included. Chronic pancreatitis may present like pancreatic cancer, but it is also a risk factor for developing pancreatic cancer.

b. Exclusion Criteria

- Patients diagnosed with other malignancies including lymphoma and lung cancer because they may have metastatic disease to the pancreas. Patients with irreversible coagulopathies because risk of bleeding is too high. Patients with cystic lesions of pancreas because these are treated and staged differently than adenocarcinoma.

c. Recruitment

- Dr. Chabot who performs > 90% of pancreatic resections at CPMC will be asked to refer patients to the study. Letters will be sent to the surgeons and gastroe nterolo gists at all the CPMC referral hospitals. No specific minority recruitment is required.

d. Subject Enrollment

While patients are being consented for EUS, they will also be asked if they want to participate in this study. Abdominal CT must done in all patients prior to enrollment to rule out distant metastasis. Patients will be told that if they are randomized to the lymph node biopsy group and their biopsy results are positive, then they will be referred back to their primary physician to discuss further management.

E. EUS FNA procedure

As described by previously[8], a linear array echoendoscope will be used to biopsy lymph nodes. Lymph nodes will be biopsied regardless of echo appearance (i.e. benign appearing nodes will also be sampled). A clinical pathologist will be present to assure adequate tissue sampling.

F. Risks and Benefits

The main risk of endoscopy is perforation (1/1,000). Conscious sedation with Demerol and versed has a risk of over-sedation, but patients will be closely monitored during procedures. The risk of fine-needle aspiration of lymph nodes is bleeding and infection although these risks are very small. There is a theoretical risk of "tract" seeding during biopsy of malignancies. The benefit for the patient is that unnecessary surgery with high morbidity and mortality may be avoided, and the patient may more quickly be able to pursue alternative non-surgical therapies. Patients who go on to surgery may be more likely to benefit from pancreatic resection.

G. Compensation and Costs to Subjects

Patients will have no additional costs. Patients will be compensated for travel time.

[8] Bhutani, MS. et. al. "A comparison of the accuracy of echo features during endoscopic ultrasound and endoscopic ultrasound guided fme-needle aspiration for diagnosis of malignant lymph node invasion." Gastrointestinal Endoscopy. 45 (6) 474-479, 1997 June.