Endoscopic Ultrasound, Magnetic Resonance Imaging And Computed Tomography For Preoperative Loco Regional Staging Of Pancreatic Cancer

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A. Study Purpose and Rational.

Pancreatic adenocarcinorna is the fourth leading cause of cancer death in both men and women in the United States. Approximately 30,000 people in the United Sates are diagnosed each year, and each year 30,000 people die from the disease. The dismal prognosis of the disease is clearly depicted by the fact that its incidence approximates its mortality. The only hope for cure is resection of the tumor prior to metastatic spread of the disease and, in most centers, surgical intervention is only offered to those patients without evidence of distant or even loco-regional metastasis. In fact, only 5-22% of patients are considered candidates for resection at the time of initial evaluation.[1] As the treatment and prognosis offered the patient therefore rely heavily upon accurate tumor staging and the reliable detection of loco-regional lymph node and vascular invasion, consistent and accurate radiographic characterization of the tumor anatomy is imperative.

Various imaging modalities are currently available for pancreatic cancer staging, including transabdominal ultrasound (US), computed tomography (CT), positron emission tomography (PET), magnetic resonance imaging (MRI) and endoscopic ultrasonography (EUS). Although US, and standard CT and MRI are often used to detect pancreatic cancer and follow advanced disease, their sensitivities and resolution are not sufficient to detect small masses or lymph node and vascular involvement. PET, although very useful for the detection of covert and distant metastatic spread, also lacks the resolution required for loco-regional staging. High-resolution helical CT, high resolution NMI and EUS have emerged as the most accurate loco-regional staging modalities, but have been inadequately evaluated individually or compared head-to-head. In addition, despite advances in the quality of images produced by all of these modalities, no individual technique has achieved sufficient sensitivity and specificity in the current literature to avoid using a combination of methods in most cases. As a result, there is no consensus about the algorithm of diagnostic imaging that should be used preoperatively, and no understanding of the accuracy such an algorithm could produce.

In the initial studies, EUS was shown to be more sensitive for vascular and lymph node invasion than CT, [2-6] though these were performed with long outdated equipment and are difficult to make relevant today. More recent studies with high-resolution helical CT have had varying results, perhaps due to better quality CT images. [7-24] However, small sample sizes, inconsistent patient populations, and varying gold standards, EUS criterion and measured outcomes, again make these studies less applicable to clinicians today. In addition, this variability is likely related to the experience and skill of the individual endoscopists performing the studies as it has been shown that the accuracy of EUS is extremely operator dependent, and that even within one operator, the accuracy of EUS increases with increasing experience. [7] The overall accuracy for determination of resectability in these studies has ranged from 67 to 96 %, and 41 to 85% for EUS and CT, respectively. [2-27]

More recently, there have been a few studies that include NMI as a preoperative staging technique, again with variable results (accuracy for resectability of about 75-96%). [28-32] The most recent manuscript to include MRI is the only previous head-to-head comparison of MRI, helical CT, and EUS to date. [28] It included 62 patients who were to go to surgery, including those with known distant metastasis who were candidates for palliative intervention. All patients got at least two *of* the three imaging techniques in the two weeks prior to surgery and pathology at surgical resection or exploration was used as the gold standard. The overall accuracies for resectability in this cohort were

67%, 83% and 75% for EUS, CT and *NMI,* respectively. This study found that CT had the highest accuracy in TNM staging (46%) vascular invasion (83%), peri-pancreatic soft tissue and organ involvement (74%) and distant metastasis (88%), and EUS had the high accuracy in lymph node staging (65%) and assessment *of* tumor size (85%).

Limitations of this study are that a less advanced MR1 machine was used (1.0 Tesla), as well as a very outdated EUS probe (Olympus GF-UM20). In addition, it was performed in a mixed patient population. Including those patients with known distant metastases (12 of the 62 total patients, 19%) that are by definition out of the purview of the EUS device clearly favored the more global imaging devices such as CT in the determination of overall resectability. On the other hand, those patients who were determined by several of these imaging techniques to be locally unresectable were excluded, likely increasing the prevalence of respectability in the population. In addition, although all of these patients went to surgery, 10 had explorations with biopsy of various structures instead of full resections, likely leading to substantial sampling error in those patients.

As there is no data supporting any of these modalities as the standard of care for preoperative staging, they are often used in combination in our institution and throughout the country. Columbia is in a unique position to begin to answer questions as to which modality is the best for pre-operative staging in general and when specific anatomic regions are in questions as it has three very experience endoscopists who stage pancreatic cancer with EUS over 50 times annually. We have a state of the art MRI machine with a 3.0 Tesla magnet and a very powerful pancreas protocol including liver and pancreas MRI, MRV, MRA and MRCP. In addition, we have a group of pancreatic surgeons who perform over 70 Whipple procedures for pancreatic cancer per year. These surgeons, unlike most other centers, also resect tumors with evidence of loco-regional spread because they believe that the morbidity and mortality of the procedure, which usually prohibits this approach in less experienced centers, are low enough that the small benefit in months of survival (probably 18 to 20 months as compared to 8 to 10 months without resection in our center as per unpublished data from CUMC) outweighs the risks of the procedure. This will allow our study population to be more diverse than only those with resectable disease while maintaining surgical pathology as the gold standard of diagnosis in all cases. The combination of these factors affords us a unique opportunity to determine, when performed at their best, what the superior test is for preoperative pancreatic cancer staging.

We therefore propose to prospectively determine the overall accuracy, sensitivity and specificity of EUS, MRI and CT in the loco-regional determination of resectability, in a larger group of patients and with more advanced technology than has been studied to date. In addition, we will compare these modalities in their overall accuracy as well as compare their ability to identify tumor involvement in specific anatomical regions, namely the peri-pancreatic soft-tissue structures, lymph nodes and vasculature.

B. Study Design

The primary aim of this prospective study is determine and compare the overall accuracy, sensitivity and specificity of EUS, NMI and CT in the preoperative determination of locoregional pancreatic cancer unresectability, as defined by any extra-pancreatic extension of the tumor. All study subjects will have EUS, CT and MRI within the two weeks prior to surgery. Pathological analysis of the resected surgical specimens will be used as the gold standard of diagnosis. Secondary outcomes will include the same calculations in those patients with specific anatomical involvement including the peri-pancreatic soft tissue, lymph nodes and vascular structures.

Statistical analysis will include calculation of the accuracy (true positives plus true negatives divided by the total number of patients), sensitivity (the number of true positives divided by the number of true positive plus false negatives) and specificity (true negatives divided by true negatives plus false positives) of each technique for overall unresectability, as well as each anatomic region described above. These accuracies will then be compared with the McNemar's chi square test [Q = (B-C)2 / B+C] to

determine whether any test is significantly better overall or in specific anatomic situations. A total of 160 subjects will be enrolled in total. The power calculation is as follows:

	Test 1		
Test 2		Correct	Incorrect
	Correct	A	B
	Incorrect	C	D

Ratio of accuracy of better test: B/B+C

-minimum meaningful result about be ratio of 0.75

Chi squared: 2n = 8 (p1q, + P2q2/effect) + 2/effect + 2

p, = 0.75 (as assumed from above)

P2 = 0.5 (the null hypothesis that there is no difference between the two tests)

n = 33 (number of patients in which the 2 compared tests must be discordant)

Assumed accuracies based upon discussions with experts using the current technology:
EUS 90%, MRI 80%, CT 70%

Number possibly discordant between EUS and MRI 10-30%, mean 20%

20% of 160 (total number to recruit) = 32 (approximate number needed to be discordant)

C. Study Procedure.

Each patient will be recruited when it is determined that they will proceed to surgical resection of their pancreatic cancer. At our institution, criteria for surgical management include no evidence of widely metastatic disease (including to the liver), pre-operative neo-adjuvant chemotherapy for those patients with the suggestion of loco-regional spread of various imaging modalities followed by surgery and strait to surgery for all other patients. Patient data including age, sex, race, ethnicity, and the agent and duration of neo-adjuvant chemotherapy, when applicable, will be collected. EUS, MRI and CT will be performed on patients who consent to the study in the two weeks prior to surgery and after the conclusion of any chemotherapy that they may have prior to the operation. The endoscopists and radiologists interpreting the EUS, MRI and CT images will be blinded to the results of the other studies. The surgeons, however, will know the results of both studies as their knowledge of the anatomy of the tumor is critical to their surgical technique. The pathologist will be blinded to the results of the pre-operative imaging studies.

The imaging procedures will be performed per standard protocol:

1. **EUS**: Conscious sedation will be used in all patients. The location and staging of the pancreatic mass will be determined with a 12 MHz radial scanning endosonography scope (GFUM160, Olympus America, Inc. Melville, N.Y.). The scope will be inserted until the second portion of the duodenum and images of the pancreas and surrounding structures will be acquired as the scope with withdrawn through the duodenum and stomach. Lymph node involvement will be defined as round shape, homogenous echogenicity, relative hypoechointensity or size >20mm. Fine needle aspiration of a lymph node with standard

technique will be done when the endoscopists believes it is required to definitively determine the status of a lymph node. Criteria for vascular invasion will include loss of the hyperechoic vessel wall/tumor interface for at least I cm, direct visualization of tumor in the vascular lumen or non-visualization of a major portal vessel in the presence of collateral vessels. All EUS images will be read by all three endoscopists at the conclusion of all procedures to maximize blinding.

2. **MRI**: MRI, MRV, MRA and MRCP images with and without gadolinium contrast will be performed with the 3 Tesla MRI machine available. Specific images acquired will include routine pancreas MRI, coronal single shot fast spin echo (for bright fluid for cysts and common bile duct), axial single shot fast spin echo (for bright fluid), axial 3D NMI with fat saturation (LAVA) before, during and after gadolinium contrast administration (for images of the pancreas as well as for involvement of the superior mesenteric vein, and portal veins and arteries), post gadolinium coronal 2D NMI with fat sat (for an overall screen of abdomen and pelvis), and post gadolinium high resolution MRCP. All MRI images will be read by one experienced radiologist (M.P.) at once, blinded to patient information and the results of other investigations. Criteria for vascular invasion will include soft tissue masses partially obliterating the peri-vascular fat, soft tissue masses circumferentially obliterating peri-vascular fat or when total or partial vascular occlusion is present. Lymph node involvement will be defined as nodes greater than 10mm in diameter. MRI will not be performed in patients with contraindications to the procedure, such as metal prostheses or implants, or with known hypersensitivity to gadolinium.
3. **CT**: High-resolution helical CT with oral and iodinated intravenous contrast that includes thin cuts through the pancreas and an arterial as well as delayed portal phase of the scan so as to view contrast in each vascular bed. As with NMI, all images will be independently read by an experienced radiologist who is blinded to all other results. Criteria for vascular and lymph node involvement will be identical to those for NMI. CT will not be performed in patients with known hypersensitivity to iodinated dye or with serum creatinine over 2.0.

The likely duration of the study will be two years in order to ensure that the appropriate number of study subjects is recruited. Each patient will be involved for a maximum of two weeks, as each imaging technique must be performed in the two week prior to surgery.

D. Study Drugs

Not applicable

E. Medical Devices

The EUS, MRI and CT equipment used in this study are all approved for use in this clinical setting. Please see the Study Procedures section for specific equipment details.

F. Study Questionnaires

Not applicable.

G. Study Subjects

Inclusion criteria will include a pathologically confirmed diagnosis of pancreatic adenocarcinorna and the plan for operative resection of their tumor, ability to have at least two of the three imaging techniques (see Study Procedures for contraindications to each test), age over 18, the ability to sign informed consent. Patients will be excluded if they have evidence of widely metastatic disease to organs

other than the peri-pancreatic lymph, vascular and connective tissue surrounding the pancreas, or are not operative candidates at the time of study enrollment due to medical comorbities or patient wishes to defer surgery.

As pancreatic cancer affects men with only a small preponderance when compared to women (1.3: 1.0), we anticipate an approximately equal recruitment of men and women. Racial and ethnic groups, as well as non-English speaking populations are desired. Given that the population of upper Manhattan comprises a large percentage of the patient base of Columbia Presbyterian, and there is a 1.7: 1.0 ratio of incidence in black men compared to the general population, we anticipate at least a 25% recruitment of racially and ethnically diverse individuals.

H. Recruitment of Subjects

Study participants will be identified through the following mechanisms: outpatient clinics and physician practices at CUMC, physician or patient self-referral, inpatient consultations, and genetic counselors. The patient identified by a physician will be approached by that health care provider and asked to participate in the study. Individuals recruited by a non-physician health care provider will be referred to one of the investigators participating on the study.

I. Confidentiality of Study Data

All study data from the same individual will be assigned an identifying number that is unique to this protocol. The number will correspond to the year of accrual and the consecutive order of accrual. Medical record numbers, social security numbers, and names will not be attached to demographic, radiographic or pathological data. Data obtained will be stored on secure servers.

J. Potential Conflicts of Interest

There are no potential conflicts of interest.

K. Location of the Study

All patient interaction will be conducted in either inpatient or outpatient clinical care areas of the Columbia University Medical Center. The outpatient locations will consist of the outpatient facilities used by the individual investigators of the study, or accruing physicians caring for the protocol individuals.

L. Potential Risks

There are no risks associated with this study, as the imaging and surgical interventions involved will all be consistent with the standard clinical management of the individual.

M. Potential Benefits

There are no immediate benefits to the individual participating in this study. The long term potential benefits to the study participants are that the results of this study may impact their future diagnostic and therapeutic decisions is additional staging or surgical intervention is indicated.

N. Alternative Therapies

Not applicable.

O. Compensation to Subjects

Not applicable.

P. Costs to Subjects

Not applicable.

Q. Minors as Research Subjects

Not applicable.

R. Radiation or Radioactive Substances

Not applicable.

S. References

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