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Linear-array EUS improves detection of pancreatic lesions in high-risk individuals: a randomized tandem study

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Abstract

Background—Studies comparing linear and radial EUS for the detection of pancreatic lesions in an asymptomatic population with increased risk for pancreatic cancer are lacking.

Objectives—To compare pancreatic lesion detection rates between radial and linear EUS and to determine the incremental diagnostic yield of a second EUS examination.

Design—Randomized controlled tandem study.

Setting—Five academic centers in the United States.

Patients—Asymptomatic high-risk individuals (HRIs) for pancreatic cancer undergoing screening EUS.

Interventions—Linear and radial EUS performed in randomized order.

Main Outcome Measurements—Pancreatic lesion detection rate by type of EUS, miss rate of 1 EUS examination, and incremental diagnostic yield of a second EUS examination (second-pass effect).

Results—Two hundred seventy-eight HRIs were enrolled, mean age 56 years (43.2%), and 90% were familial pancreatic cancer relatives. Two hundred twenty-four HRIs underwent tandem radial and linear EUS. When we used per-patient analysis, the overall prevalence of any pancreatic

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lesion was 45%. Overall, 16 of 224 HRIs (7.1%) had lesions missed during the initial EUS that were detected by the second EUS examination. The per-patient lesion miss rate was significantly greater for radial followed by linear EUS (9.8%) than for linear followed by radial EUS (4.5%) ($P = .03$). When we used per-lesion analysis, 73 of 109 lesions (67%) were detected by radial EUS and 99 of 120 lesions (82%) were detected by linear EUS ($P < .001$) during the first examination. The overall miss rate for a pancreatic lesion after 1 EUS examination was 47 of 229 (25%). The miss rate was significantly lower for linear EUS compared with radial EUS (17.5% vs 33.0%, $P = .007$).

Limitations—Most detected pancreatic lesions were not confirmed by pathology.

Conclusion—Linear EUS detects more pancreatic lesions than radial EUS. There was a “second-pass effect” with additional lesions detected with a second EUS examination. This effect was significantly greater when linear EUS was used after an initial radial EUS examination.

INTRODUCTION

EUS is a standard imaging test for the pancreas that can detect asymptomatic pancreatic cancer and its precursor lesions in high-risk individuals (HRIs).^{1–8} In particular, in a large multicenter, blinded, 3-way comparative trial, EUS and magnetic resonance imaging (MRI) detected more small cystic and solid lesions than pancreas protocol CT.¹

The 2 basic types of US endoscopes used in clinical practice today are radial and linear array echoendoscopes.^{9,10} Radial array echoendoscopes produce US images perpendicular to the axis of the endoscope tip with a 360-degree scanning range. The circumferential images produced are often easier for a novice endosonographer to interpret. Radial EUS is not suitable for EUS-guided biopsy sampling and therapeutic interventions. Linear array echoendoscopes produce US images parallel to the long axis of the endoscope, with scanning ranges between 100 and 180 degrees. Linear array echoendoscopes offer a distinct advantage over the radial array echoendoscopes because FNA and therapeutic interventions are able to be performed through the instrument channel under real-time guidance.

Linear EUS is often favored by many endosonographers for pancreatic imaging, regardless of whether or not FNA is required.^{11,12} This preference may be based on prior training and experience. No studies support the systematic use of linear over radial EUS for screening and early detection of pancreatic cancer and its precursors. The studies that compare radial and linear EUS for diagnosing and staging pancreatic malignancies^{13–17} and for diagnosing chronic pancreatitis have variable conclusions.^{18,19} For example, radial and linear array EUS were found to be comparable for the EUS-based diagnosis of chronic pancreatitis.^{18,19}

Tandem colonoscopy studies involving experienced colonoscopists have demonstrated an average 22% miss rate for colon adenoma detection with the first colonoscopy examination.^{20–29} The Cancer of the Pancreas Screening (CAPS) 3 study previously reported an overall EUS miss rate for pancreatic lesions of 6.9% compared with MRI, but the overall miss rate for detection of pancreatic lesions after 1 EUS needs to be better elucidated. Furthermore, the potential advantage of 1 type of echoendoscope (radial vs linear) over another is uncertain, even among highly experienced endosonographers. In a

population at high risk for pancreatic cancer, missed lesions might negatively impact on the detection of neoplasia and ultimately influence patient care.

The primary aims of the study were to compare pancreatic lesion detection rates of radial array and linear array EUS in a well-defined, asymptomatic, high-risk population undergoing pancreatic screening. We also sought to determine the incremental diagnostic yield of a second EUS examination and the miss rate of radial versus linear EUS.

METHODS

Study design

The CAPS 3 study was a prospective cohort study involving 5 academic centers in the United States. All subjects underwent both radial and linear EUS examinations of the pancreas by expert endosonographers and contrast-enhanced pancreatic CT and MRI. This was a randomized tandem study embedded in the CAPS 3 study. Subjects were randomized to initial radial or linear EUS, followed immediately (during the same sedated procedure) by a second pancreatic EUS examination with the alternate type of echoendoscope.

The institutional review boards of all 5 participating institutions approved the research protocol. All subjects provided written informed consent. The CAPS 3 study was registered on the National Institutes of Health clinicaltrials.gov website (NCT00438906).

Study population

Consecutive asymptomatic high-risk individuals (HRIs) who consented to be part of the CAPS 3 study and underwent an EUS examination at 1 of the 5 participating centers (Johns Hopkins Hospital, Baltimore, Md; Mayo Clinic, Rochester, Minn; University of California, Los Angeles, Calif; Dana Farber Cancer Institute/Brigham and Women's Hospital, Boston, Mass; and MD Anderson Cancer Center, Houston, Tex) were screened for eligibility. HRIs included those with Peutz-Jeghers syndrome, familial breast-ovarian cancer patients with at least 1 affected first- or second-degree relative with pancreatic ductal adenocarcinoma, and relatives of patients with familial pancreatic cancer with at least 1 pair of affected first-degree relatives, with at least 1 of the affected a parent or sibling. Exclusion criteria included the inability to provide informed consent, prior pancreas screening, Karnofsky performance status of less than 60, any suspicion of pancreatic disease based on prior history, prior pancreas surgery, severe medical illness, bleeding diathesis or thrombocytopenia, renal insufficiency, allergic reaction to radiographic contrast material, morbid obesity, severe claustrophobia, and upper GI tract obstruction.¹

MRI

Gadolinium- and secretin-enhanced MRCP was performed according to a standardized protocol. All MRI sequences were obtained at a minimum of 1.5 Tesla (GE, Waukesha, Wisc or Siemens, Malvern, Pa) using a phased-array torso coil. Human synthetic secretin (.2 mg/kg; ChiRhoClin, Inc, Burtonsville, Md) was given intravenously. T2-weighted acquisitions for the MRCP were acquired in the coronal plane. Five postsecretin MRCP images were acquired every minute starting 1 minute after secretin administration. The

individual slices and reconstructed maximum intensity projections before and after secretin were used for viewing the 3-dimensional MRCP. In addition, axial breath-hold unenhanced and dynamic contrast-enhanced (.1 mmol/kg body weight), T1-weighted, 3-dimensional, fat-suppressed, spoiled gradient echo imaging were acquired in the arterial, portal venous, and delayed phases (20 seconds, 70 seconds, and 3 minutes, respectively).¹

CT

Standardized pancreatic protocol CT scans were performed on a Somatom Flash Dual Source scanner (Siemens). Patients drank 1000 mL of water over a 30-minute period before the scan with the last 250 mL immediately before the study. Intravenous contrast was injected at 4 to 5 mL/s using a volume of 100 to 120 mL of Omnipaque-350 or Visipaque-350 (GE Healthcare, Inc, Princeton, NJ) depending on patient renal function and/or age. Dual-phase imaging at 30 and 60 seconds was obtained routinely.

Scan parameters were as follows: 120 kVp, and body quality reference mass of 320 mAs using Care Dose (Siemens Healthcare, Malvern, Pa) and .6-mm detectors. Images were reconstructed with thin and thick sections at .75-mm thin sections reconstructed at .5-mm intervals and 3-mm thick sections reconstructed at 3-mm intervals. Images were analyzed with postprocessing software, including axial imaging, multiplanar reconstruction, and 3-dimensional rendering. The 3-dimensional reconstruction was accomplished with both volume rendering and maximum intensity projection techniques.¹

EUS

Before initiation of the CAPS 3 study, the terminology, definitions of various pancreatic lesions (including mass, cyst, dilated pancreatic duct), and the associated EUS image criteria were standardized in the 2004 CAPS Consensus National Cancer Institute/Specialized Program in Research Excellence sponsored workshop (Bethesda, Md).³⁰ Endoscopists with expertise in EUS performed all procedures. An expert endosonographer was defined as an endoscopist who had performed greater than 2000 independent EUS examinations with at least 500 examinations of each type of EUS (radial array and linear array). EUS imaging was performed using a mechanical or electronic radial array (GFUM20, GFUE160-AL5; Olympus Corporation, Center Valley, Pa; EG-3670URK; Pentax Medical, Montvale, N.J.) and/or a linear array echoendoscope (CFUC140P, SSD-Alpha5 or Alpha10; Olympus Corporation; EG-3870UTK; Pentax Medical). HRIs underwent tandem radial and linear EUS in a randomized order. Randomization was performed using a random-numbers table and sequentially numbered, opaque, sealed envelopes at each site. All EUS procedures were performed with sedation according to the standard medical care guidelines at each institution. The same endosonographer performed both EUS examinations. If a lesion was detected after the second radial EUS examination, the linear array echoendoscope was reintroduced if FNA was needed. Endosonographers were blinded to the results of CT and MR examinations until after they had completed the tandem EUS examination. CT and MRI occurred 1 to 2 days before the EUS examinations to potentially allow for FNA of detected lesions.³¹

In the CAPS 3 study, a detected lesion was defined as a pancreatic abnormality (mass or dilated main pancreatic duct) visualized on any 1 of the 3 imaging tests used in screening. For this study the analysis was limited to comparison of masses. The pancreatic masses detected by EUS were classified as cystic or a solid. The type, size, and location of each lesion were recorded on a pancreas map for precise documentation for both radial and linear EUS. The CAPS 3 study involved baseline screening with 3 imaging modalities to determine the prevalence of pancreatic abnormalities in a high-risk cohort. Subsequent patient follow-up was performed according to the institution-specific standard of care.¹

Statistical methods

The χ^2 test, exact test, *t* test, Wilcoxon rank-sum test, and 3-way ANOVA were performed for categorical and numeric variables, where appropriate. The McNemar test was used to analyze paired data. Two-tailed *P* < .05 were considered statistically significant. All statistical analyses were performed using the Stata software package, version 11 (Stata Corp, College Station, Tex). The sample size for this study embedded within the CAPS 3 study was based on the estimated population prevalence of 15% of HRIs with a detectable pancreatic neoplasm.¹

RESULTS

Table 1 summarizes the baseline characteristics of the HRIs included in the study. In total, 278 asymptomatic HRIs with a mean age of 56.1 years (range, 25.6–86.5) were enrolled. The HRIs were predominantly white (92%) and belonged to the familial pancreatic cancer risk group (90%). The remaining 10% were mutation carriers. Of the 278 HRIs, 54 (19%) had only 1 radial or linear EUS. These 54 patients were enrolled in the first phase of the CAPS 3 study, and this tandem study was added as an amendment to the study protocol. The remaining 224 HRIs (81%) who had tandem radial and linear EUS provided the data for this study (Fig. 1).

Of the 224 study patients, 194 had imaging with the Olympus EUS system and the remaining with the Pentax EUS. Of those who had EUS examinations with the Olympus system, 90 (46.4%) had mechanical radial array echoendoscopy. Subgroup analysis showed no statistically significant differences in the radial versus linear lesion miss rate (per-patient analysis) between the 2 EUS systems or the type of radial echoendoscope (*P* = nonsignificant).

Per-patient analysis

Two hundred eighty-three pancreatic lesions were detected by all imaging tests (EUS, CT, and/or MRI) in the 224 subjects who had tandem EUS examinations. Of these lesions, 229 were detected by EUS. The overall prevalence of any pancreatic lesions was 43.2% (100/224) when using a per-patient analysis. Most of these subjects with detectable pancreatic lesions had cystic lesions (91/100; 91.0%) with a mean size of .6 cm (range, 0.1–2.4). Those patients with solid masses detected underwent FNA (*n* = 12 patients) or surgery (*n* = 5 patients). The cytologic diagnoses of patients who had FNA were pancreatic neuroendocrine tumors (*n* = 3) and benign lymph nodes. The pathologic diagnosis of the 5

patients who had surgery is detailed in the primary study¹ and included intraductal papillary mucinous neoplasms, multifocal pancreatic intraepithelial neoplasia, and lobulocentric atrophy.

The average number of pancreatic lesions in HRIs detected during screening by any EUS was 2 (range, 1–15). In the 224 HRIs who had 2 tandem EUS procedures, 16 (7.1%) had lesions missed during the initial EUS that were detected by the second EUS examination (second-pass effect). This was greater when linear followed initial radial EUS. Eleven of these 16 HRIs (9.8%) with missed lesions had radial followed by linear (radial/linear) EUS and 5 of 16 (4.5%) had linear followed by radial (linear/radial) EUS ($P = .03$).

Per-lesion analysis

Two hundred twenty-nine pancreatic lesions were identified by any EUS in the 224 HRIs who underwent tandem EUS examinations (Fig. 2). Among the patients who underwent radial followed by linear EUS, 109 lesions were detected. The first radial EUS yielded 73 of 109 lesions (67%) and the subsequent linear EUS yielded an additional 36 lesions (Fig. 3). Hence, the per-lesion miss rate for radial EUS was 33%. In the linear followed by radial group, 120 lesions were detected. The first linear EUS detected 99 of 120 lesions (82.5%) and the subsequent radial EUS yielded an additional 21 lesions (17.5%) (Fig. 4). Hence, the perlesion miss rate for a pancreatic lesion during a second examination with the linear EUS was significantly lower than that for the radial EUS (17.5% vs 33%, $P = .007$).

The missed lesions were distributed throughout the pancreas ($P = \text{nonsignificant}$) (Table 2). The average size of the lesions missed by radial EUS was small (mean, .57 cm; range, .3–1.2) and similar ($P = .63$) to those missed by linear EUS (mean, .47 cm; range, .3–.6).

DISCUSSION

EUS is a powerful imaging technique for evaluating pancreatobiliary disease. The selection of type of echoendoscope (radial vs linear array)^{9,10} has been left to the discretion and preference of the individual endosonographer. The anticipated need for tissue sampling may also influence the choice of echoendoscope. Radial EUS is typically preferred for luminal GI cancer staging, but there appears to be an increased use of linear EUS over time.^{11,12} Anecdotally, some endosonographers believe that linear EUS provides superior quality and more complete imaging of the pancreas.

Our study validates the current trend in increasing preference for the linear array echoendoscope for pancreatic imaging. We report for the first time a novel concept of a “second-pass effect” for EUS, with a second EUS examination detecting additional, mostly small, cysts regardless of type of echoendoscope in 7.1% of patients overall. Our study results seem surprising given the known high sensitivity of EUS for pancreatic masses, but the findings are akin to the second-pass effect for tandem colonoscopy, with an average of 22% miss rates for adenomas.^{20–29} The lesion miss rate appears to be lower for EUS than for colonoscopy. Furthermore, despite the known miss rate for colon adenomas with a single colonoscopy examination, tandem colonoscopy examinations are not routinely performed.

We also showed that linear EUS detects more pancreatic lesions when compared with radial EUS during the initial examination in a cohort of asymptomatic HRIs undergoing screening. The *per-patient* EUS miss rate for experienced endosonographers was 9.8% for the initial radial EUS and 4.5% for the initial linear EUS, when a second EUS was performed back to back. The incremental detection rate for pancreatic lesions during screening EUS was significantly greater when the linear EUS (33%) was used as the second imaging modality after the initial radial EUS examination (17.5%).

Although it appears concerning that the overall EUS lesion detection rate was only 81%, the overall *per-patient* detection rate in our high-risk cohort was 93%. As previously reported, EUS is still the best imaging modality for detecting pancreatic lesion when compared with CT and MRI. The original study published by the CAPS 3 study comparing CT, MRI, and EUS performed in every patient and interpreted in a blinded fashion showed that EUS had the highest detection rate for pancreatic lesions (majority cystic) with 36% diagnostic yield (per patient) for EUS versus 33% and 11% for MRI and CT, respectively. EUS detected 79% of all detected lesions seen by any imaging study when using a per-lesion analysis, whereas MRI detected 77% and CT detected only 14%.¹ Most importantly, no malignant lesions were missed with any EUS examination. Although all missed lesions were small cysts, subjects at high risk for pancreatic cancer typically undergo routine surveillance with repeat imaging regardless of baseline findings.² In prior studies, we have shown in high-risk patients who have had surgery that most of these small cysts are benign branch duct or incipient intraductal papillary mucinous neoplasms or larger visible pancreatic intraepithelial neoplasia.¹⁻⁴ Low-grade pancreatic intraepithelial neoplasia (1 and 2) are common in the general population,³² similar to the 2% to 4% prevalence of branch duct intraductal papillary mucinous neoplasms detected by routine abdominal imaging.^{33,34}

There are several strengths of the current study. It was an embedded study within a large, multicenter study involving 5 centers using site-specific EUS equipment and standardized EUS nomenclature. Second, the order of EUS examination was randomized, with each patient serving as his or her own control. Third, the study cohort involved asymptomatic HRIs enrolled in a screening program who underwent complete imaging of the pancreas in a standardized protocol, and all pancreatic abnormalities were recorded in a detailed prospective fashion.

Our study also had several limitations. All EUS examinations were performed by expert endosonographers, which may affect the generalizability of the findings to all clinical settings. EUS is also operator dependent, but there is good interobserver agreement among endosonographers for pancreatic cysts³⁰ in this study population.¹ The variability in EUS echoendoscopes and processors may have also increased variability in lesion detection. However, it was not possible to use the same echoendoscopes across all 5 sites, and the generalizability of our findings might then be limited. Furthermore, the use of a mechanical array radial echoendoscope could have impacted the study findings. One randomized study comparing mechanical versus electronic radial EUS reported better image quality for the latter (using a subjective visual analog scale).³¹ However, our subgroup analysis did not reveal a statistically significant difference in pancreatic lesion detection rates along scope types.

Next, the lack of the use of contrast agents and/or elastography in this study could also have affected the overall detection rate and characterization of the detected pancreatic lesions. However, because each subject served as his or her own control, it is likely that the lack of image enhancements would not impact the differences in the detection rates within the same subject or between groups. Also, there is a theoretical concern for double counting of lesions on EUS. Although it is always possible, we believe it is unlikely that the EUS examination double counted lesions because of the standardized detailed mapping, the expertise of the endosonographers, and the subsequent correlation with MRI and CT.

Finally, most of the asymptomatic pancreatic lesions detected in our screening study could not be verified by pathology as most could not be aspirated because of very small size and were not surgically resected because of lack of concerning features. However, this is also the case for most small incidentally detected pancreatic cysts in HRIs as well as the general population. The clinical significance of missed minute cystic lesions in this highly selected patient group is uncertain.

In conclusion, in patients at high risk for pancreatic cancer, linear EUS detects more pancreatic lesions and has a lower miss rate than radial EUS. It should be considered as the echoendoscope of choice when imaging the pancreas.

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Abbreviations

CAPS 3	Cancer of the Pancreas Screening 3
HRI	high-risk individuals
MRI	magnetic resonance imaging

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Figure 1.
Study schema. *HRI*, high-risk individuals.

Figure 2.
Study flow diagram.

Figure 3. Small cystic lesion missed by initial radial EUS examination detected by subsequent linear EUS examination.

Figure 4. Small cystic lesion missed by initial linear EUS examination detected by subsequent radial EUS examination.

TABLE 1

Patient characteristics (n = 278)

Characteristic	Value
Risk group	
Familial pancreatic cancer	250 (90%)
<i>BRCA2</i> + relative with pancreatic cancer	25 (9%)
Peutz-Jeghers syndrome	3 (1%)
Race	
White	256 (92.1%)
African American	3 (1.1%)
Native American	2 (.7%)
Asian/Pacific Islander	1 (.4%)
Other	16 (5.8%)
Gender	
Male	143 (51.4%)
Mean age: 56.1 y (range, 25.6–86.5)	
50 y	197 (70.9%)
Final diagnosis by cytology, histology and clinical follow-up ¹	
Confirmed or suspected branch duct IPMN	82
Combined IPMN	2
Pancreatic endocrine tumor	3
Isolated main pancreatic duct dilation	4
Indeterminate benign cyst	1
Lymph nodes	6

IPMN, Intraductal papillary mucinous neoplasm.

TABLE 2

Characteristics of lesions missed during tandem EUS examination (per-lesion analysis)

Size	Head of pancreas	Body of pancreas	Tail of pancreas	Total number
<i>Missed by initial radial EUS (n = 36)</i>				
<5 mm	3	7	7	17
5–10 mm	7	7	4	18
>10 mm	0	1	0	1
Total number	10	15	11	36
<i>Missed by initial linear EUS (n = 21)</i>				
<5 mm	3	5	2	10
5–10 mm	4	3	4	11
>10 mm	0	0	0	0
Total number	7	8	6	21

P = nonsignificant.