EDITORIAL

Pancreatic EUS: the linear strikes back

Endosonography is a well-established procedure that was introduced almost 34 years ago. Early studies demonstrated the ability of a high-speed, rotating scanner mounted on the tip of an oblique-viewing endoscope to visualize the pancreatic and biliary anatomy.[1] This EUS instrument had a 360° rotating mechanical probe that scanned perpendicular to the longitudinal axis of the endoscope. In the esophagus and proximal part of the stomach, it provided images comparable with those available from CT. For this reason, it was believed that endoscopists unfamiliar with transabdominal US anatomy would be able to interpret the images. Since this first report a critical mass of studies has defined the role of EUS in the diagnosis and staging of pancreatic disorders, with great impact in the clinical management of pancreatic cancer.

In the early 1990s, linear echoendoscopes entered clinical practice.[2] These instruments provided 2 substantial improvements in EUS: electronic probes with great potential for future technical development (not available with the mechanical technology used for the radial design) and the ability to safely guide—in "real time"—a needle passed throughout the working channel of the instrument into a target zone for EUS-guided FNA. This is possible because the scanning field of the echoendoscopic probe lies on the same longitudinal plane as the endoscope. Many experts in radial EUS were strongly opposed to this new technology, citing supposed "major disadvantages" such as the smaller, linear-oriented, sector image and the difficulty in defining even normal anatomic relationships. For these reasons, linear EUS was pronounced inferior for the diagnosis and staging of pancreatic cancer. However, demonstration of the efficacy and safety of EUS-FNA changed the echoendoscope from a purely diagnostic tool to a device capable of cytologic diagnosis of pancreatic lesions and subsequently of therapeutic interventions.[3] Two very different approaches to linear EUS examinations have evolved; although European centers have largely substituted radial instruments for linear instruments to evaluate the pancreas, in Japan and the United States pancreatic investigation is still performed primarily with radial probes, linear echoendoscopes being relegated to the role of aspiration only. This radial EUS–dominated approach probably explains the difficulty experienced by many echoendoscopists in the United States in trying to obtain adequate FNA pancreatic specimens, as evidenced by a 2007 survey by the American Society for Gastrointestinal Endoscopy in which the reported success rate was only 71%.[4] During the past 20 years, several trials have compared radial and linear EUS probes for evaluating both benign and malignant pancreatic disease. In 1997, Gress et al[5] found no significant differences between the 2 systems in TNM staging of pancreatic cancer, especially with reference to vascular involvement. Recently, a Japanese study compared radial and linear probes for evaluating specific anatomic sites in the pancreatobiliary system, showing that the linear EUS probe is superior to the radial probe in most areas, with the exception of the main duodenal papilla.[6]

Although in high-risk individuals the algorithm considering both EUS and magnetic resonance imaging should be preferred, EUS is still the best single modality to detect a pancreatic lesion, but a negative EUS result is unable to completely exclude the presence of a pancreatic lesion in a patient with clinical suspicion of pancreatic cancer.

Until now, no study has compared the 2 systems (ie, radial vs linear EUS) for detecting focal pancreatic lesions. In this issue of *Gastrointestinal Endoscopy*, Shin and colleagues[7] report a randomized, controlled, tandem study designed to answer this question. Five academic centers involved in the CAPS-3 Study (American Cancer of the Pancreas Screening Consortium) enrolled a population of asymptomatic individuals at high risk for the development of pancreatic cancer.[8] These patients underwent screening pancreatic EUS to evaluate the detection and miss rates of the 2 different types of probe. In the study design, patients were randomized to initial radial or linear EUS followed, while they were under the same sedation, by a second pancreatic evaluation performed with the other probe. In each study center, both EUS procedures were performed by a single endosonographer with a reported experience of at least 500 examinations with each kind of probe.

0016-5107/$36.00
http://dx.doi.org/10.1016/j.gie.2015.05.027

The instruments used were mechanical and electronic radial probes and linear probes with state-of-the-art echographic systems. The study endosonographers agreed on definitions of the various pancreatic lesions and recorded each definition in every patient on a "pancreas map" used to compare the results of the 2 probes. Two hundred twenty-four high-risk individuals were enrolled in the study; tandem procedures were performed, mostly with the Olympus EUS system (Olympus, Tokyo, Japan), and almost half of those with a mechanical radial probe. Two hundred eighty-three lesions were found in 100 of the 224 patients (45%) enrolled. Tandem EUS examination detected 229 of 283 lesions, with a miss rate of 19%. Ninety-one patients had cystic lesions of the pancreas, and 17 had solid lesions; of those, 12 underwent EUS-FNA and 5 went directly to surgery, with a final diagnosis of neuroendocrine tumor, intrapancreatic lymph nodes, intrapancreatic mucinous neoplasm, and pancreatic intraepithelial lesion(s) of the ductal epithelium. In the study population of 224 high-risk individuals, the first EUS examination failed to detect lesions in 7.1% of patients, and this miss rate was greater in the radial-first protocol (11 vs 5 patients $P = .03$) as compared with the linear-first protocol. In a per-lesion analysis, the radial-first protocol failed to detect 33% of lesions, whereas the first linear examination showed a per-lesion miss rate of 17.5%, significantly lower than the previous ($P = .007$).

We congratulate the authors on a well-designed and well-executed trial, which had 3 important results: EUS had a significant miss rate for focal pancreatic lesions, "tandem" EUS reduced this miss rate, and, finally, linear EUS was significantly better than radial EUS in this setting. There are potential biases in this study that need to be taken into account. First, we have to consider the study population: an asymptomatic group of individuals at high risk for pancreatic cancer. They were participants in a state-of-the-art screening program conducted by recognized experts in the field. The finding of a 1-mm to 2-mm cyst was considered a suspicious-looking pancreatic lesion, and at least 2.9 lesions per patient were identified (range, 1-15 lesions). This setting is completely different from a population of patients in whom there is a clinical suspicion of pancreatic cancer based on previous diagnostic imaging, abnormal serologic markers of malignancy, or both. Here the identification of a single (usually) solid lesion is the goal of the EUS examination, and the anticipated miss rate would be considerably less than 7.1%, but still not negligible, contravening previous data reporting a 100% negative predictive value of EUS to depict pancreatic cancer.[9] A second potential bias relates to the experience of the endosonographers who participated in the study. The authors emphasize that their experts had a large experience of both radial and linear pancreatic EUS examination (≥500). Unfortunately, we cannot accurately determine their level of expertise in using each of the 2 systems: we don't know whether the majority of these experts routinely use the radial probe for diagnosis and reserve the linear probe for FNA only. If this is the case, their level of experience in evaluating the pancreatic parenchyma should be considered far inferior with the linear probe in comparison with the radial probe. Perhaps some of the endosonographers had already abandoned the radial probe in favor of the linear probe and returned to the former only for the purpose of this study? The fact that almost half of the procedures performed with a radial Olympus probe were done with an old mechanical instrument, rather than with a newer and considerably improved electronic radial EUS endoscope, supports this hypothesis. Because endosonographers have consistently favored 1 instrument over another (ie, the linear vs the radial probe), it seems unlikely that they would be equally skilled with both devices. A third possible cause of bias is the "mapping" of lesions in the pancreas; this may be "easy" for an expert endosonographer, but we are offered no data on interobserver agreement, intraobserver agreement, or both on the reproducibility of locating lesions with the use of radial and linear probes. The range of lesions found in the study was 1 to 15; could multiple small cysts have been overestimated, or approximately counted, biasing the final numbers? Because we would like these study results to be reproducible in a clinical setting of patients with sporadic pancreatic cancer, it would be better to focus on patients with a solitary lesion. In the study population, 43 of 100 patients (43%) had a single lesion detected (both cystic and solid); in this setting the radial-first protocol missed 9 lesions (9/43 = 20.9%), whereas the linear-first protocol missed only 2 (2/43 = 4.6%). However, if we consider only patients with single solid lesions, the reported miss rate for both protocols is 1 of 17. The authors suggest that their "tandem EUS" approach taken in this study reduces the miss rate for pancreatic lesions, but what if the endosonographer, rather than the endoscope, were to be changed between the first and second evaluations? This could be the focus of another study using the same group of experts.

So, what are the "take-home" messages from this study? Although in high-risk individuals the algorithm considering both EUS and magnetic resonance imaging should be preferred, EUS is still the best single modality to detect a pancreatic lesion; but a negative EUS study result is unable to completely exclude the presence of a pancreatic lesion in a patient with a clinical suspicion of pancreatic cancer. Whenever this happens, it would be justified to perform another pancreatic EUS using another instrument or, perhaps, a different endosonographer, ideally with the patient under the same sedation. In centers with a high volume of pancreatic procedures, linear EUS probes should be the first choice for examining the pancreatic parenchyma.

DISCLOSURE

All authors disclosed no financial relationships relevant to this publication.

Maria Chiara Petrone, MD
Endosonography Unit
Paolo Giorgo Arcidiacono, MD, FASGE
Gastrointestinal Endoscopy Unit
Gastroenterology and Gastrointestinal Endoscopy Unit
San Raffaele Scientific Institute
Vita Salute San Raffaele University
Milan, Italy

Abbreviations: CT, computed tomography; EUS-FNA, EUS-guided fine-needle aspiration; CAPS, American Cancer of the Pancreas Screening Consortium; NET, neuroendocrine tumor; IPMN, intraductal papillary mucinous neoplasm; PANin, pancreatic intraepithelial neoplasia; NPV, negative predictive value.

REFERENCES

1. Hisanaga K, Hisanaga A, Nagata K, et al. High speed rotating scanner for transgastric sonography. AJR Am J Roentgenol 1980;135:627-9.
2. Vilmann P, Khattar S, Hancke S. Endoscopic ultrasound examination of the upper gastrointestinal tract using a curved-array transducer. A preliminary report. Surg Endosc 1991;5:79-82.
3. Vilmann P, Jacobsen GK, Henriksen FW, et al. Endoscopic ultrasonography with guided fine needle aspiration biopsy in pancreatic disease. Gastrointest Endosc 1992;38:172-3.
4. Savides TJ, Donohue M, Hunt G, et al. EUS-guided FNA diagnostic yield of malignancy in solid pancreatic masses: a benchmark for quality performance measurement. Gastrointest Endosc 2007;66:277-82.
5. Gress F, Savides T, Cummings O, et al. Radial scanning and linear array endosonography for staging pancreatic cancer: a prospective randomized comparison. Gastrointest Endosc 1997;45:138-42.
6. Kaneko M, Katanuma A, Maguchi H, et al. Prospective, randomized, comparative study of delineation capability of radial scanning and curved linear array endoscopic ultrasound for the pancreaticobiliary region. Endosc Int Open 2014;02:E160-70.
7. Shin EJ, Topazian M, Goggins M, et al. Linear-array EUS improves detection of pancreatic lesions in high-risk individuals: a randomized tandem study. Gastrointest Endosc 2015;82:812-8.
8. Canto MI, Hruban RH, Fishman EK, et al. American Cancer of the Pancreas Screening (CAPS) Consortium. Frequent detection of pancreatic lesions in asymptomatic high-risk individuals. Gastroenterology 2012;142:796-804.
9. Klapman JB, Chang KJ, Lee JG, et al. Negative predictive value of endoscopic ultrasound in a large series of patients with a clinical suspicion of pancreatic cancer. Am J Gastroenterol 2005;100:2658-61.