

Endoscopic ultrasound in clinical practice

Daniel Keter, Ehud Melzer

Department of Gastroenterology and Liver Diseases, Kaplan Medical Center, Rehovot, and the Hebrew University School of Medicine, Jerusalem, Israel.

Acta Gastroenterol Latinoam 2008;38:146-151

Summary

Endoscopic ultrasonography (EUS) is an accurate technique for the diagnosis and staging of benign and malignant lesions in the gastrointestinal tract and the mediastinum. EUS overcomes the limitations of other imaging diagnostic methods and gives the possibility to obtain tissue for histologic diagnosis (EUS guided FNA). The most useful indications of EUS are differentiation of submucosal tumors, staging for neoplasia, examination of the pancreato-biliary system and therapeutics. EUS can distinguish extrinsic compressions from intramural lesions and defines their nature (solid, cystic or vascular) and origin. EUS is useful for local staging of esophageal, gastric, duodenal, and rectal cancer using the TNM (tumor, node, metastases) system, as well as for diagnosing and staging of pancreatic lesions. The addition of EUS-guided FNA has improved the ability to detect malignant lymph node invasion. EUS is also highly sensitive for the diagnosis of choledocholithiasis, avoiding unnecessary danger of diagnostic ERCP. New therapeutic indications of EUS include drainage of pancreatic pseudocysts and abscesses and celiac plexus block and neurolysis. EUS has become an indispensable diagnostic method in gastroenterological everyday practice and should be part of most endoscopy units.

Keywords: echoendoscopy, indications

La ecoendoscopia en la práctica clínica Resumen

La ultrasonografía endoscópica (EUS) es una técnica precisa para el diagnóstico y estadío de lesiones benignas y malignas en el tracto gastrointestinal y el mediastino. La EUS supera las limitaciones de otros métodos de diagnóstico de imágenes y da la posibilidad de obte-

ner tejido para diagnóstico histológico (EUS guiado FNA). Las indicaciones más útiles de la EUS son la diferenciación de tumores submucosos, en estadío de neoplasia, examen y terapéutica del sistema pancreato-biliar. La EUS puede distinguir compresiones extrínsecas de lesiones intramuros y define su naturaleza (sólido, quístico o vascular) y el origen. La EUS es útil para el estadío local de cáncer del esófago gástrico duodenal y rectal usando el sistema de TNM (tumor, nódulo, metástasis), así como para el diagnóstico y estadío de lesiones pancreáticas. La incorporación de EUS-FNA guiado ha mejorado la capacidad de detectar la invasión de los nódulos linfáticos malignos. La EUS también es altamente sensible para el diagnóstico de colédoco litiasis, evitando el peligro innecesario de diagnóstico de ERCP. Nuevas indicaciones terapéuticas de la EUS incluyen el drenaje de pseudoquistes pancreáticos y abscesos, y bloqueo del plexo celiaco y neurolysis. La EUS se ha convertido en un método de diagnóstico indispensable en la práctica diaria gastroenterológica y debe formar parte de la mayoría de las unidades de endoscopia.

Palabras claves: ecoendoscopia, indicaciones

Endoscopic Ultrasound (EUS) was initially developed in the early 1980's. The idea was to improve the limitations of the Abdominal Ultrasound and Computed Tomography in the imaging of the pancreas.

Today, EUS has considerably expanded the gastrointestinal endoscopy daily practice, as well as other fields of medicine, let us say, "how could we live without it".

The indications for EUS are numerous as it overcomes several disadvantages of transabdominal ultrasound. The EUS probe lies nearer to the organs that are examined and therefore higher US frequencies may be used, leading to a much higher resolu-

Correspondencia: Daniel Keter
E-mail: keterdan@zahav.net.il

tion. In addition, the problem of gas in between the transabdominal probe does not exist with EUS. For these reasons EUS is highly useful to image the upper GI tract wall¹⁻² as well as the adjacent organs, namely the pancreas, biliary tract, mediastinum and all peri-esophageal and peri-gastric tissue.³

Many studies have shown EUS as a safe and accurate diagnostic technique for the diagnosis, staging and sampling of a variety of benign and malignant lesions.

EUS-FNA has become an indispensable adjunct to the technique since 1993, when it was shown to be feasible and safe to obtain tissue diagnosis in the majority of the lesions that could be detected by EUS.

Technique: endoscopic ultrasound is performed with a mechanical or electronic ultrasound transducer that is built into the tip of a flexible endoscope. A balloon with water-filling encases the ultrasound transducer at the tip of the endoscope and helps to overcome the difficulty of imaging in an air-filled lumen.

Two different types of instrument are available: a radial scanner 270-360 degree, perpendicular to the long axis of the scope, i.e. like a computed tomography (CT) axial cut, and an electronic linear array endoscope, 130-180 degree sectorial axis, that enables EUS guided fine needle aspiration (FNA) and biopsy of structures within or in close proximity to the GI tract. Doppler imaging in some of the endoscopes is used to determine the vascular anatomic landmarks and to identify vessels in order to avoid bleeding complications when performing FNA.

Ultrasonic frequencies (5-30 MHz) can identify lesions as small as 2-3 mm and delineate 5-9 (depending on the US frequency) layers of the GI tract wall corresponding with the histological layers. Normally 5 layers are demonstrated (from the inner to outer) - superficial mucosa, deep mucosa, submucosa, muscularis propria, and serosa.

Miniprobe ultrasound probes are thin devices that can be passed through the working channel of a conventional endoscope. These probes exert high frequency (20-30 MHz), circumferential image, and demonstrate up to nine layers of the GI tract with a limited tissue depth of 1-3 cm. They are mostly used to assess narrow esophageal strictures and flat lesions, difficult to locate with a regular echoendoscope, as in early gastric cancer, and submucosal lesions.

The assessment of small submucosal (non-protru-

ding) esophageal varices (undiagnosed by videoendoscopy) can be demonstrated very well with EUS probes that avoid the compression on the varices when using EUS with water filled balloon, resulting in a false negative examination to detect varices.

EUS most useful indications

- 1) Differentiation of sub-mucosal tumors.
- 2) Staging of neoplasia.
- 3) Examination of the pancreato-biliary region.
- 4) Therapeutics.

Differentiation of submucosal tumors (SMTs)

The diagnosis of SMT may be impossible with conventional endoscopic and radiological imaging.

EUS can distinguish extrinsic compressions from real intramural lesions and defines their nature (solid, cystic or vascular).

The sensitivity and specificity of EUS for differentiating between SMT and extraluminal compression, are high, in one these were study were 92% and 100%, compared to only 87% and 29% for endoscopy, respectively.⁴

The differentiation between malignant and benign SMT is problematic as well.

EUS malignancy indicators are size >3 cm, heterogeneous echo-structure, irregular margins and shape, associated lymph nodes.⁵

EUS-FNA in gastro-intestinal stromal tumor (GIST) raised the accuracy of EUS alone (78%) to 91% with histopathology.

Benign diagnosis of GIST based in histopathology is only tentative and needs strict follow-up.

GIST malignancy EUS-FNA accuracy rise to 100% when the Ki-67 LI stain is used.

Staging gastrointestinal luminal cancers.

EUS is useful local staging of esophageal, gastric, duodenal, and colorectal cancer using the TNM (tumor, node, metastases) system.

EUS is the most accurate modality for local T staging, meaning local extent of tumor.

T staging is as follows:

T1 tumors involve the mucosa or submucosa.

T2 extension into the muscularis propria but not beyond.

T3 extension beyond the muscularis propria.

T4 denotes local invasion of surrounding structures, vessels.

N staging is reported as N0, N1, N2, but N-staging

is much less accurate, only 60% to 80% accuracy.

Echo-features of nodes suggestive of malignancy are: diameter greater than 1cm, round shape, hypo-echogenicity, and distinct margins. Yet, these are inconclusive signs due to inter-observer variation and their accuracy is limited.

EUS FNA has improved the ability to detect malignant lymph node invasion. It can be done in subcarinal, aortopulmonary window, para-aortic, para-tracheal, celiac axis, and para-pancreatic lymph nodes.

EUS-guided FNA has a Sensitivity of 80% and specificity of about 94% for the diagnosis of malignant lymph node invasion.⁶

Esophageal cancer EUS is the best modality for staging early and advanced carcinoma.

In Esophageal Adenocarcinoma itself, EUS plays a critical role in loco-regional staging.

EUS has been shown to be significantly more accurate than CT in identifying T stage⁷ accuracy over 89%.⁸

Different studies agree on EUS superiority versus CT scan for loco-regional staging, particularly celiac nodes, best detected by EUS.

The prognosis is related with T and N staging and the presence of celiac trunk lymph node invasion

In the evaluation of nodal involvement, EUS has been shown to be accurate when EUS-guided FNA is performed on suspicious nodes. A large prospective study reported a sensitivity, specificity, and accuracy of 92%, 93%, and 92% respectively for presence of malignant lymph nodes.⁹

After neo-adjuvant chemo-radiotherapy for locally advanced disease, EUS is increasingly being used to evaluate pathologic responders. A reduction in tumor thickness has been shown to correlate with therapeutic response.¹⁰

Early carcinoma limited to mucosa (T1m) or submucosa (T1sm), both with excellent prognosis after treatment.

Diagnosis is made with high-frequency probe introduced by using a standard endoscope.

Treatment: EMR (endoscopic mucosal resection) for small lesions (<2 cm in diameter or < one third of circumference involved).¹¹⁻¹²

Advanced esophageal cancer:

Different studies agree on EUS superiority versus CT scan for loco-regional staging, particularly celiac nodes, best detected by EUS.

The prognosis is related with T and N staging and the presence of celiac trunk lymph node invasion.

Strict correlation between EUS staging and subsequent therapeutic strategies.

In particular, advanced neoplasm as T4 and/or M1 (i.e, celiac lymph nodes metastases) can be selected for palliative therapies, avoiding surgical intervention, that would not change the prognosis.

Many studies evaluating EUS concluded that sensitivity for the T and N staging of esophageal cancer is about 85-95% and 70-80%, respectively.¹³⁻¹⁴

Gastric cancer

Advanced gastric cancer.

EUS staging helps assess the resectability and prognosis of advanced gastric cancer.

EUS is more accuracy than CT in the T staging (92% vs 48%).¹⁵ This has recently become more important as neo-adjuvant therapy is now the standard of care for patients with locally advanced gastric cancer. CT, is the best method to detect distant metastases, as part of standard evaluation of gastric cancer.

Early gastric cancer: studies mostly from Japan, describes the high accuracy of EUS in predicting endoscopic resectability and clinical impact as gastrectomy can be spared, specially in elderly, with comorbidities.¹⁶

Gastric lymphoma and large gastric folds .

EUS is an accurate technique for the differential diagnosis of large gastric folds.

Gastric lymphoma, linitis plastica, Menetrier's disease, inflammatory conditions, and gastric varices, some of the common etiologies.

MALT (gastric mucosa associated lymphoid tissue), EUS is very accurate for the diagnosis. Can predict remission after helicobacter pylori eradication therapy, can monitor response to therapy, evaluate the need of additional therapy, and early detection of relapse.¹⁷

Pancreatic cancer

Survival is dismal and radical resection are possible in only a minority of patients with pancreatic malignancy.

As only 25% of patients seem to be operable and less than 5% are potentially cured, it is mandatory to be able to select those patients who will most benefit from surgery and avoid operation of all others.

EUS adopted by many authors as the best technique for loco-regional staging in pancreatic cancer indicating the optimal treatment strategy.

Harewood and Wiersema¹⁸ demonstrated that EUS-FNA was the less costly strategy for staging compared to CT-guided FNA and surgery.

Their study results confirmed that EUS had greater sensitivity than CT in detecting a mass (99% vs 57%).

In one of the studies, EUS-FNA sensitivity for malignant disease was as high as 94%, with a specificity for benign disease of 71% and accuracy of 92%.

EUS estimated accuracy of 93% to 100% compared with 53% to 90% for CT, MRI, ERCP, or angiography.¹⁹⁻²⁰

Resectability of pancreatic cancer is influenced directly by the presence of vascular invasion. EUS detects venous invasion better than arterial, and invasion of the portal vein and splenic confluence better than invasion of the superior mesenteric vein and artery.²¹

EUS is not an infallible method for detecting a pancreatic carcinoma and factors for a false negative EUS examination included chronic pancreatitis, a diffusely infiltrating adenocarcinoma, a prominent ventral/dorsal split and a recent episode of acute pancreatitis.

Periampullary cancer

Periampullary tumors include ampullary, distal choledochal, pancreatic head, and duodenal tumors.

Due to low 5-year survival, 40%, accurate preoperative staging can prevent unnecessarily radical resection, as is with pancreatic cancer.

In many studies, EUS superior to CT and ultrasound in T staging (EUS 50%, CT 5%, ultrasound 0%) as well as for detecting lymph node metastases (EUS 50%, CT 33% and ultrasound, 0%).²²

Intraductal ultrasound is more accurate than conventional EUS for periampullary tumors, less than 3 cm in diameter.²³

Pancreatic cysts

EUS is the best technique for the diagnosis of pancreatic cysts, but not reliable for the differential diagnosis between benign and malignant. EUS is limited and the inter-observer agreement is low.²⁴

Brugge et al.²⁵ prospectively collected the results of EUS imaging, cyst fluid cytology, and cyst fluid tumor markers (CEA, CA 72-4, CA 125, CA 19-9, and CA 15-3) using histology as a final diagnostic standard.

Out of 341 pts, cyst fluid CEA demonstrated the greatest area under the curve analysis of tumor markers, for differentiation of mucinous vs non-mucinous cystic lesions.

The accuracy of CEA (79%) was significantly greater than the accuracy of EUS morphology (51%) and cytology (59%) ($P < 0.05$).

These tumors may be suspected after the onset of clinical symptoms, related to hormonal activity.

Neuroendocrine tumors may be highly symptomatic even when they are quite small (sometimes several mm). CT, MR angiography with selective hormonal sampling are not sensitive enough and sometimes invasive and cumbersome. EUS has a high sensitivity and specificity for detecting small lesions particularly, insulinomas.²⁶

Biliary Disease

EUS is very sensitive for the detection of choledocholithiasis, and when the clinical suspicion of common bile duct stones is low or intermediate, can obviate the need for diagnostic endoscopic retrograde cholangio pancreatography (ERCP), a more invasive procedure with a significant rate of complications and should not be used anymore as a diagnostic procedure. In contrast, if CBD stones are detected by EUS, therapeutic ERCP can be done immediately at the same sitting, or immediately later on when unavailable at that moment.

Napoleon et al,²⁷ in a study of 238 such patients, followed prospectively for at least 12 months, demonstrated a negative predictive value of 97% for common bile duct stones.

Magnetic resonance cholangio-pancreatography (MRCP) is also an established diagnostic method in these patients.

In a comparative study between EUS and MRCP in 43 pts with suspicion of CBD stones, using ERCP or intraoperative cholangiography as the gold standard, the accuracy of EUS was 97% and that of MRCP was 82%.²⁸

For the examination of the proximal choledocus, the use of higher frequency (12-20 MHz), intraductal ultrasound (IDUS), performed over a guidewire at ERCP appears to be superior than standard EUS.

Chronic pancreatitis

EUS can detect chronic pancreatitis at an early stage, being more sensitive than CT, ERCP, and functional tests.

Rectal cancer

EUS, is the most accurate imaging modality for T and N staging in rectal cancer.

EUS evaluates tumor invasion depth and sphincters involvement, determining treatment approach (eg, transanal vs invasive surgery, abdominal perineal resection vs preoperative neoadjuvant chemoradiation). The accuracy is 85% for T staging and 75% in N staging. 29).

EUS and Therapeutic applications

EUS guided drainage of pancreatic pseudocysts and abscesses.

With an operative echoendoscope, with a wide working channel 3.2mm that allows passage of 8.5 French stents, Giovaninni et al,³⁰ described the technique.

Coeliac plexus neurolysis.

For the treatment of intractable pain in patients affected from pancreatic carcinoma (or less commonly severe chronic pancreatitis).

The technique is feasible and safe. Concerns about durability of the effects.

Pain scores were significantly lower 2 weeks after the procedure, an effect that was sustained for 24 weeks after adjustment for morphine and use of adjuvant therapy.³¹⁻³²

Summary

EUS has shown a great development in the last 20 years, for the imaging and staging of mass tumoral lesions within and in close vicinity with the gastrointestinal (GI) tract.

In addition to other more conventional imaging techniques, as helical computed tomography and magnetic resonance imaging, EUS can assess suspected lesions by this methods, and specifically may help to differentiate between benign and malignant lesions of the upper abdominal tract, staging malignant tumors of esophagus, (lung and mediastinum), stomach, pancreas, and rectum, before either surgical and/or oncological treatment. Can help to exclude choledocholithiasis, avoiding the need for endoscopic cholangiopancreatography (ERCP) as a diagnostic tool, and using it only therapeutically.

EUS has evolved from only diagnostic imaging tool to fine needle aspiration (FNA) EUS guided, for tissue diagnosis.

Therapeutically, can provide pain relief, through guided celiac plexus neurolysis and pancreatic pseudocyst drainage.

By now investigational techniques, is fine-needle injection (FNI) of antineoplastic agent directly into a cancer.

The EUS learning for endoscopists according to general consensus, is longer than that for ERCP, as shown in a few studies.

The demand for EUS increases, and based on EUS indications in three major US centers, estimated that the potential number of EUS procedures is approximately 300 per million population per year

References

1. Caletti G, Bolondi L, Labo G. Ultrasonic endoscopy - the gastrointestinal wall. *Scand J Gastroenterol* 1984;102:5-8.
2. Kimmey MB, Martin RW, Haggitt RC, Wang KY, Franklin DW, Silverstein. Histologic correlates of gastrointestinal ultrasound images. *Gastroenterology* 1989;96:433-441.
3. Nickl NJ, Bhutani MS, Catalano M, Hoffman B, Hawes R, Chak A, et al. The American Endosonography Club. Clinical implications of endoscopic ultrasound: the American Endosonography Club Study. *Gastrointest E* 1996;44:371-377.
4. Rosch T, Kapfer B, Will U, Baronius W, Strobel M, Lorenz R, et al. Accuracy of endoscopic ultrasonography in upper gastrointestinal submucosal lesions: a prospective multicenter study. *Scand J Gastroenterol* 2002; 37:856-862.
5. Chak A, Canto MI, Rosch T, Dittler HJ, Hawes RH, Tio TL, et al. Endosonographic differentiation of benign and malignant stromal cell tumors. *Gastrointest Endosc* 1997; 45:468-473.
6. Harada N, Wiersema M, Wiersema L. Endosonography guided fine-needle aspiration biopsy (EUS FNA) in the evaluation of lymphadenopathy: staging accuracy of EUS FNA versus EUS alone [abstract]. *Gastrointest Endosc* 1997;45:AB31
7. Lightdale CJ, Kulkarni KG. Role of endoscopic ultrasonography. In the staging and follow-up of esophageal cancer. *J Clin Oncol* 2005;23:4483-4489.
8. Rice TW, Blackstone EH, Adelstein DJ, et al. Role of clinically determined depth of tumor invasion in the treatment of esophageal carcinoma. *J Thorac Cardiovasc Surg* 2003; 125:1091-1102.
9. Wiersema MJ, Vilmann P, Giovannini M, Chang, et al. Endosonography guided fine-needle aspiration biopsy: diagnostic accuracy and complication assessment. *Gastroenterology* 1997;112:1087-1095.
10. Willis J, Cooper GS, Isenberg G, et al. Correlation of EUS measurement with pathologic assessment of neoadjuvant therapy response in esophageal carcinoma. *Gastrointest Endosc* 2002;55:655-661.
11. Ell C, May A, Gossner L, Pech O, Gunter E, Mayer G, et al. Endoscopic mucosal resection of early cancer and high-grade dysplasia in Barrett's esophagus. *Gastroenterology* 2000;118:670-677.

12. Nijhawan PK, Wang KK. Endoscopic mucosal resection for lesions with endoscopic features suggestive of malignancy and high-grade dysplasia within Barrett's esophagus. *Gastrointest Endosc* 2000;52:328-32.
13. Botet JF, Lightdale CJ, Zauber AG, Gerdes H, Urmacher C, Brennan MF. Preoperative staging of esophageal cancer: comparison of endoscopic US and dynamic CT. *Radiology* 1991;181:419-425.
14. Ziegler K, Sanft C, Zeitz M, Friedrich M, Stein H, Haring R, Riecken EO. Evaluation of endosonography in TN staging of oesophageal cancer. *Gut* 1991;32:16-20.
15. Botet JF, Lightdale CJ, Zauber AG, Koch J, Gerdes H, Winawer SJ, Urmacher C, et al. Preoperative staging of gastric cancer: comparison of endoscopic US and dynamic CT. *Radiology* 1991;181:426-433.
16. Ohashi S, Segawa K, Okamura S, Mitake M, Urano H, Shimodaira M, et al. The utility of endoscopic ultrasonography and endoscopy in the endoscopic mucosal resection of early gastric cancer. *Gut* 1999;45:599-604.
17. Caletti G, Zinzani PL, Fusaroli P, Buscarini E, Parente F, Federici T, et al. The importance of endoscopic ultrasonography in the management of low-grade gastric mucosa-associated lymphoid tissue lymphoma. *Aliment Pharmacol Ther* 2002;16:1715-1722.
18. Harewood GC, Wiersema MJ. A cost analysis of endoscopic ultrasound in the evaluation of pancreatic head adenocarcinoma. *Am J Gastroenterol* 2001;96:2651-2656.
19. Legmann P, Vignaux O, Dousset B, Baraza AJ, Palazzo L, Dumontier I, et al. Pancreatic tumors: comparison of dual-phase helical CT and endoscopic sonography. *AJR Am J Roentgenol* 1998;170:1315-1322.
20. Yasuda K, Mukai H, Nakajima M, Kawai K. Staging of pancreatic carcinoma by endoscopic ultrasonography. *Endoscopy* 1993;25:151-155.
21. Brugge WR, Lee MJ, Kelsey PB, Schapiro RH, Warshaw AL. The use of EUS to diagnose malignant portal venous system invasion by pancreatic cancer. *Gastrointest Endosc* 1996;43:561-567.
22. Chen CH, Tseng LJ, Yang CC, Yeh YH. Preoperative evaluation of periampullary tumors by endoscopic sonography, transabdominal sonography, and computed tomography. *J Clin Ultrasound* 2001;29:313-321.
23. Menzel J, Hoepffner N, Sulkowski U, Reimer P, Heinecke A, Poremba C, et al. Polypoid tumors of the major duodenal papilla: preoperative staging with intraductal US, EUS, and CT. A prospective, histopathologically controlled study. *Gastrointest Endosc* 1999;49:349-357.
24. Ahmad NA, Kochman ML, Lewis JD, Ginsberg GG. Can EUS alone differentiate between malignant and benign cystic lesions of the pancreas? *Am J Gastroenterol* 2001;96:3295-3300.
25. Brugge WR, Lewandrowski K, Lee-Lewandrowski E, et al. Diagnosis of pancreatic cystic neoplasms: a report of the cooperative pancreatic cyst study. *Gastroenterology* 2004;126:1330-1336.
26. Scheiman JM, et al. Endoscopic ultrasound is highly accurate and directs management in patients with neuroendocrine tumors of the pancreas. *Am J Gastroenterol* 2000;95:2271-2277.
27. Napoléon B, Dumortier J, Keriven-Souquet O, et al. Do normal findings at biliary endoscopic ultrasonography obviate the need for endoscopic retrograde cholangiography in patients with suspicion of common bile duct stone? A prospective follow-up study of 238 patients. *Endoscopy* 2003;35:411-415.
28. de Lédinghen V, Lecesne R, Raymond JM, et al. Diagnosis of choledocholithiasis: EUS or magnetic resonance cholangiography? A prospective controlled study. *Gastrointest Endosc* 1999;49:26-31.
29. Rosch T. Endoscopic ultrasonography. *Endoscopy* 1994;26:148-168.
30. Giovannini M, Pesenti C, Rolland AL, Moutardier V, Delperro JR. Endoscopic ultrasound-guided drainage of pancreatic pseudocysts or pancreatic abscesses using a therapeutic echo endoscope. *Endoscopy* 2001;33:473-477.
31. Gunaratnam NT, Sarma AV, Norton ID, Wiersema MJ. A prospective study of EUS-guided celiac plexus neurolysis for pancreatic cancer pain. *Gastrointest Endosc* 2001;54:316-324.
32. Gress F, Schmitt C, Sherman S, Ciaccia D, Ikenberry S, Lehman G. Endoscopic ultrasound-guided celiac plexus block for managing abdominal pain associated with chronic pancreatitis: a prospective single center experience. *Am J Gastroenterol* 2001;96:409-416.