MINI-REVIEW

Endoscopic Ultrasound Staging of Upper Gastrointestinal Malignancies

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Abstract

Since 1980, endoscopic ultrasound (EUS) has been used as an important tool for the evaluation of malignant diseases in hollow viscus and bilio-pancreas, as well as sub-epithelial tumors. The high-resolution capacity and low penetration depth of EUS make it possible to obtain highly detailed images of the gastrointestinal wall and immediate surroundings to a depth of 4-5 cm. Thus, over the past 35 years, EUS succeeded to modify management in significant number of cases and is now considered a gold standard tool for many gastrointestinal diseases, especially in the pancreatico-biliary tract, and adjuvant needle insertion now allows access to remote lesions that were difficult to reach in the past. With the growing spectrum of indications, tissue sampling for diagnostic purposes has become common. In this review, we aim to highlight the expanding spectrum of EUS indications and uses in staging of upper gastrointestinal malignancies, especially esophageal, gastric and ampullary tumors.

Keywords: Endoscopic ultrasound - upper gastrointestinal malignancies - cancer staging

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Introduction

Endoscopy, ultrasound, and computed tomography (CT) have revolutionized the field of clinical gastroenterology in recent decades. By combining a high-frequency ultrasound probe with an endoscope, the so-called "echoendoscope" or "endoscopic ultrasound (EUS)", clearly detailed imaging of the structures close to the gastointestinal (GIT) wall was achieved. In 1980, the first mechanical radial EUS was applied clinically (DiMagno et al., 1980).

Endoscopic ultrasound (EUS) has recognized as an essential imaging modality for the evaluation of malignant diseases of the hollow viscus and bilio-pancreas, as well as sub-epithelial tumors. Although significant differences in opinions were observed, EUS managed during the past 35 years to modify managing decisions regarding a big number of cases (Lee et al., 2014).

The indications for EUS are determined by the anatomic conditions and the technical capabilities of the equipment. The high-resolution capacity and low penetration depth of EUS make it possible to obtain highly detailed images of the GIT wall and immediate surroundings to a depth of 4-5 cm (Byrne and Jowell, 2002).

EUS use is now considered a gold standard tool for many gastrointestinal diseases, especially pancreaticobiliary diseases, and adjuvant needle insertion allows access to remote lesions that were difficult to reach in the past. With the growing spectrum of indications, the clinical applicability of EUS has expanded to include therapeutic applications in addition to diagnostic uses, and some of these show great promise. Major breakthroughs in the technical advances of EUS technology were achieved in the last few decades, especially in scope design, accessory devices, and add-on facilities, which have placed EUS and its related maneuvers as a necessary procedure in many gastrointestinal indications (Mekky and Abbas, 2014). Here, we will try to highlight this revolution and to delineate the applications of EUS in upper gastrointestinal tract.

Indications in Cancer Staging

<u>EUS-guided Cancer staging</u>: It can detect gastrointestinal tumors arising from the mucosa, using TNM classification. EUS is also important in the diagnosis of extra-luminal malignancies, e.g. pancreatic cancer (Byrne and Jowell, 2002). Also EUS issued in the characterization of a sub-mucosal tumor that forms a bulge in conventional endoscopic images, and to determine its layer of origin, and, hence, its nature (Bhutani, 2000). The use of contrast enhanced diffusion-EUS, can differentiate hyper-vascular from hypo-vascular areas. With development of harmonic imaging methods (contrast enhanced harmonic-EUS), it also became possible to obtain better visualization of the microcirculation and parenchymal perfusion, and better differentiation of tissue enhancement for more accurate classification (Ishikawa

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Sherif El Saadany et al et al., 2010).

EUS-guided fine needle aspiration (EUS-FNA): it is the widely used indication that affects patients' diagnosis such as: (1) differential diagnosis of benign and malignant lesions; (2) Cancer staging; and (3) biopsy taking and examination to decide the best treatment regimens (Dumonceau et al., 2011). Currently, most of the recent guidelines assign EUS-FNA as an integral part of sampling of the pancreas, mediastinal lymph nodes (esophageal/ lung cancer), intra-abdominal lymph node, posterior mediastinal mass of unknown etiology, and intra-pleural/ intra-abdominal fluid. The indications for EUS-FNA have been extended to sub-mucosal tumors, small liver lesions, left adrenal masses, and suspected recurrent cancers in and adjacent to an anastomosis (Ishikawa et al., 2010). In spite of the growing list of EUS-FNA indications, a small list of contraindications should be considered (Hawes, 2010).

EUS-guided tissue elastic imaging: it represents a technical mode that allows estimation of tissue stiffness for non-invasive evaluation of fibrosis. The operating characteristics of the technique for detecting malignancy in pancreatic focal lesions reachs a sensitivity of 93%, and a specificity of 66 % (Saftoiu and Vilmann 2013). A further evaluation in the near future may enhance its diagnostic accuracy and help to avoid the need to obtain tissue for diagnosis.

Staging of Esophageal Malignancies

Clinical staging is critical for therapeutic decision making in patients newly diagnosed with esophageal cancer. In the absence of systemic metastases, the T and N status of the tumor are used to select patients for neoadjuvant therapy or primary surgery. EUS is considered the most accurate tool for T and N staging (Worrell et al., 2014) "reported accuracy of 72–76 % for T status and 66-89 % for N status". EUS-FNA improves the staging accuracy and decision making markedly (Puli et al., 2008; Low, 2011).

Determining the T stage (Figure 1): Many staging modalities have been applied for esophageal cancer diagnosis; including EUS, chest CT, MRI, and positron emission tomography (PET). Puli et al., (2008) reported that CT and MRI cannot accurately distinguish T stage of esophageal cancer because they lack the ability to differentiate layers of the esophageal mucosa.

On the other hand Familiari et al. (2005) reported that "EUS has the ability to visualize the individual histological layers of the esophagus. This approach is particularly more sensitive in evaluating local invasion of esophageal cancer than CT or PET especially with more advanced tumor (T4)".

"Once the tumor has been identified endoscopically, the echoendoscope should be carefully advanced beyond the most distal portion of the tumor. Tumors that cannot be assessed with a EUS scope due to tumor stenosis will have locally advanced disease in the majority of cases. In these situations, pre-dilatation of the tumor with EUS staging should be omitted when considering the risk of potential esophageal perforation and the patients should be referred for neoadjuvant therapy. Esophageal tumors appear as hypoechoic masses with irregular borders and penetration beyond the esophageal layers should be described. Measurement of the mass thickness should be noted as it can predict extra-esophageal extension (Brugge et al., 1997; Worrell et al., 2014).

Carcinoma in situ (Tis) is the earliest stage, in which malignant cells are confined within the epithelium and the lamina propria is intact. Attila and Faigel. (2009) stated that "When malignant cells invade the lamina propria, the tumor is then defined as a T1 lesion. T1 lesions can be subdivided into T1m (tumor invading lamina propria) and T1sm (tumor invading submucosa). Mucosal lesions are subdivided into three groups: m1, carcinoma limited to the epithelium; m2, carcinoma with invasion into the lamina propria; and m3, carcinoma with invasion into but not through the muscularis mucosa. Submucosal lesions are also subdivided into three groups: sm1, lesions with invasion into the superficial one-third of submucosa (>200 mm); sm3, lesions with invasion into the deepest one-third of submucosa; and sm2, lesions with penetration into the intermediate one-third of submucosa". EUS is not accurate in defining the T-stage of carcinoma-in-situ or superficial adenocarcinomas. So, EMR should be used in staging (Young et al., 2010).

Stage T2 tumors invade but do not extend beyond the fourth hypoechoic layer (the muscularis propria) (Puli et al., 2008). While, T3 is tumor invading adventitia, or going through the muscularis propria, and T4 is a tumor invading adjacent structures. T4 tumors were further subdivided into T4a that invades pleura, pericardium and diaphragm and T4b which invades other structures such as the trachea and aorta. T4a tumors are considered resectable while T4b tumors are considered unresectable (Edge and Compton, 2010; Rice et al., 2010). Puli et al. (2008) proved that "EUS to have a high pooled sensitivity for T staging between 81-90% with a pooled specificity of approximately 99%. The pooled sensitivity and specificity of EUS for assessing tumor depth per T stage were 81.6% and 99.4% for T1, 81.4% and 96.3% for T2, 91.4% and 94.4% for T3, and 92.4% and 97.4% for T4".

Determining the N stage: Lymph node metastasis (LMN) in esophageal cancer occurs from the superficial cancer and spreads wildly from the neck to the abdomen. The number of involved lymph nodes (instead of their location) has been found to have prognostic implications (Zhang et al., 2010). This led to a revision of the N classification to support groupings of number of positive nodes as follows: N0 (none), N1 (1–2), N2 (3–6), and N3 (\geq 7) (Rice et al., 2010). Murata et al. (2003) & Catalano et al. (1994) reported that "endoscopic ultrasonography (EUS) findings of malignant LNs showed they were more than 5-10 mm in diameter, with a distinct border, hypoechoic internal echo and round shape".

Again Murata et al. (2003) detected that "sensitivity, specificity and accuracies for the diagnosis of malignant LNs by EUS were 49-99%, 33-99% and 71-96%. The rates widely varied, because the accuracy of EUS's ability to determine malignancy were based on the evaluation of various echo features of LNs, and were dependent on the judgement of subjective observers. Therefore histological analysis is necessary for adequate treatments. Endoscopic

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ultrasonography guided fine-needle aspiration cytology (EUS-FNA) has been performed for the diagnosis of malignant LNs. EUS-FNA staging was better than EUS staging as it has no clinically obvious complications, has sensitivity 81-97%, specificity 83-100% and accuracy 83-97%" (Figure 2).

Determining the M stage: The liver is the most common site of distant metastases of esophageal cancer. Singh et al., (2009) detected that "EUS can accurately evaluate the medial two thirds of the liver for metastases but cannot reliably exclude metastases in the entire liver. CT and PET are most commonly used to evaluate for distant metastases. The role of EUS is greatest in confirming the presence of metastases in distant lymph nodes or lesions in the liver". Van Vliet et al. (2008) reported that "EUS accuracy is increased by FNA and cytological evaluation of liver lesions as small as 4 mm". Prasad et al., (2004) also, concluded that "careful examination of the liver should be performed during staging for occult metastases not identified by other imaging studies. Identification of occult lesions may be low but can change the management of the patient. Any focal, discrete hypoechoic lesion of the liver identified should be sampled by EUS".

Restaging following neo-adjuvant therapy: Accuracy of EUS after chemotherapy or Chemo-radiotherapy of esophageal cancer is lower than initial staging accuracy because of inflammation and fibrosis that remain after



Figure 1. TN Staging of Esophageal Cancer. © Copyright 2001-2015. 1800 Orleans Street, Baltimore, Maryland 21287

neo-adjuvant therapy may be indistinguishable from residual tumor and may result in over staging by EUS (Jamil et al., 2008; Ribeiro et al., 2006). However, EUS may contribute useful clinical information about treatment response and potential survival (Lightdale and Kulkarni 2005; Mesenas et al., 2008).

Staging of Gastric Malignancies

According to Mocellin et al. (2011) "Patients with gastric cancer often present with advanced disease at the time of diagnosis, which is usually unresectable. Distant metastases and/or involvement of major blood vessels usually indicate unresectability. EUS is considered as the diagnostic tool of choice for evaluation of tumor depth in gastric cancer. This holds true especially in differentiating between early to intermediate (T1-2) and advanced (T3-4) primary tumors. Gastric masses usually appear as irregular, poorly circumscribed hypoechoic masses". Tumors arising at the esophago-gastric junction, or arising in the stomach 5 cm or less from the esophago-gastric junction and crossing the esophago-gastric junction, are



Figure 2. EUS in Oesophageal Cancer. The tumour (T) has invaded through the muscularis propria (T3). A 5 mm lymph node (LN) is seen (T3N1)

Table 1. AJCC Tumor Node Metastasis TNM Classification

Designation	Description
Tumor	
Tis	In situ dysplasia or intramucosal carcinoma
T1	Tumor invades submucosa
Τ2	Tumor invades into, but not through, muscularis propria
Т3	Tumor invades through muscularis propria
T4	Tumor invades adjacent organs or visceral peritoneum
Regional Lymph nodes	
NX	Lymph nodes cannot be assessed
NO	No regional lymph node metastasis
N1	Metastasis in one to three regional lymph nodes
N2	Metastasis in four or more regional lymph nodes
Distant Metastasis	
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis or seeding of abdominal organ

*AJCC= American Committee on Cancer

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Figure 3. Endoscopic Ultrasound Image (EUS) Showing Cross-Section of Corresponding Layers in the Stomach Wall. © Copyright 2001-2015. 1800 Orleans Street, Baltimore, Maryland 21287

staged using the TNM system for esophageal carcinoma, while gastric cancer staging system applies to tumors arising in the more distal stomach, and those arising in the proximal 5 cm without crossing the esophago-gastric junction (Washington 2010; Razavi et al., 2015).

Carcinoma in situ (Tis): Choi et al., (2010; 2011) stated that "intraepithelial tumor without invasion of the lamina propria. T1Tumors confined to the mucosa and submucosa, this stage is further subdivided into T1a (Tumor invades lamina propria or muscularis mucosae) and T1b (Tumor invades submucosa). T2 stage Tumor invades muscularis propria. T3 (tumor invading the serosa), T4 (tumor infiltrating adjacent structures". Isomoto et al., (2009) and Chung et al., (2009) detected that "T3 Tumor penetrates subserosal connective tissue without invasion of visceral peritoneum or adjacent structures. T3 tumors also include those extending into the gastrocolic or gastrohepatic ligaments, or into the greater or lesser omentum, without perforation of the visceral peritoneum covering these structures. T4 Tumor invades serosa (visceral peritoneum) or adjacent structures. stage T4 is further subdivided into T4a Tumor invades serosa (visceral peritoneum) T4b Tumor invades adjacent structures such as spleen, transverse colon, liver, diaphragm, pancreas, abdominal wall, adrenal gland, kidney, small intestine, and retroperitoneum. The distinction between Tis, T1a and T1b is important in deciding whether endoscopic resection is feasible. In areas with a high prevalence of gastric cancers, such as Japan and Korea, endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) is widely employed as a safe and minimally invasive curative technique".

EUS can discriminate T1-2 from T3-4 gastric malignancy with great accuracy, with sensitivity, specificity of 86% %.91 respectively. This supports the use of EUS for the loco-regional staging of gastric cancer to improve therapeutic management of these cases (Mocellin et al., 2011).

Determining the N stage: Gastric cancer N stage classification is based on the number of regional lymph nodes as follows: N0 (none), N1 (1-2), N2 (3-6), N3 (7 or greater) (Washington 2010). In assessing LN metastasis (N staging), Puli et al., (2008) reported "lower diagnostic performance compared to T staging. The sensitivity and specificity for N1 were 58.2% and 87.2% respectively, while the sensitivity and specificity for N2 were 64.9% and 92.4% respectively". Similarly, the accuracy reported



Figure 4. TNM Staging of Gastric Cancer, Showing Depth of Invasion. © Copyright 2001-2015. 1800 Orleans Street, Baltimore, Maryland 21287

by Cardoso et al., (2012) was 64%.

In EUS, the LN metastasis is usually diagnosed based on the morphological characteristics, echogenicity and size of LN, and over half of the metastatic lymph nodes were reported to be 5mm or less in diameter (Kwee and Kwee 2009). Thus, LN size, which is most commonly utilized in N staging of EUS among the criteria in practice, is not a consistent measure of LN metastasis, and the low performance of EUS in N staging could be explained (Mönig et al., 1999; Hwang and Lee, 2014). With the advanced technology of EUS devices, EUS-guided FNA sample of LN can increase accuracy in a safe way (Hassan et al., 2010). Chen et al., (2004) detected that "the sensitivity and specificity of EUS-FNA for detecting metastatic LNs ranged from 63% to 98% and from 87.5% to 100%, respectively".

Hassan et al. (2010) reported their experience in 81 gastric cancer patients "in whom EUS-FNA was performed. Among 99 lesions, 91 (62%) lesions were found to be malignant, and in 38 of 81 patients (42%), distant metastasis was confirmed by EUS-FNA. By using EUS-FNA in the evaluation of gastric cancer patients, the treatment plan was changed in 15% of the cases, and Hassan et al concluded that EUS-FNA was a very important modality and should be integrated as a routine procedure in preoperative gastric cancer staging". Although more data is needed to definitely establish the role of EUS-FNA, this modality could be considered in the clinical setting to avoid unnecessary surgery.

Determining the M stage: EUS is not suitable for detecting distant metastases but is sensitive in evaluating portions of the liver for metastatic disease and for malignant ascites. Various studies have shown that "the detection of ascites by EUS in patients with gastric cancer is associated with peritoneal metastases. Ascites appears as an echoic, triangular shaped collections of fluid in the peri-hepatic or peri-gastric regions. FNA can be formed for cytological evaluation. Care must be taken not to cross the tumor in order to obtain the fluid. This may produce a falsely positive result and also contaminate the fluid with malignant cells" (Chu et al., 2004; Lee et al., 2005; Kaushik et al., 2006). Prophylactic antibiotics should be administered and continued post-procedure. Washington



Figure 5. TNM Staging for Lymph Node Involvement. ©Copyright 2001-2015 All Rights Reserved. 1800 Orleans Street, Baltimore, Maryland 21287

(2010) stated that "Positive peritoneal cytology is classified as M1".

Infiltrating gastric malignancies: Infiltrating malignancies of the stomach include the diffuse type of gastric adenocarcinoma (linitis plastica) and primary gastric lymphomas. EUS is important in determining the depth of involvement of these lesions. The normal gastric thickness is between 3 to 5 mm and appears thickened in infiltrating tumors.

Vander et al. (2004) detected that "EUS will usually reveal thickening limited to the first and second sonographic layer indicating a mucosal disease. For lesions involving the third and fourth sonographic layers, deep endoscopic biopsies (using a bite-on-bite technique) or full-thickness surgical biopsies are often necessary to make a diagnosis. EUS-FNA in evaluating intramural and extramural GI tract lesions showed the sensitivity, specificity, and diagnostic accuracy of EUS-FNA in diagnosing GI tract neoplastic lesions were 89%, 88%, and 89%, respectively". Another study done by Janssen (2009) reported "T stage accuracy between 80-92% and N stage between 77-90%. The study also added that, FNA with flow cytometry of the aspirate may aid in the detection of metastatic lymph nodes and guide further management".

Restaging of gastric tumor after neo-adjuvant chemotherapy: The accuracy of restaging by EUS for T and N classification was not as good as pathological data after neoadjuvant chemotherapy. Over staging was the main form of inaccuracy in EUS T classification. This due to the difficult differentiation between the inflammation and the residual tumor after chemotherapy. Also, edema and fibrosis which may complicate chemotherapy result in gastric wall destruction. Therefore, EUS imaging cannot accurately distinguish between these changes and residual tumor tissues resulting in over staging (Guo et al., 2014).

Staging of Ampullary Tumors

Carcinomas of the ampulla of Vater are rare and can arise from the major papilla, pancreas, duodenum and the common bile duct. EUS is useful in evaluating the depth of invasion of ampullary tumors and it aids in determining whether endoscopic resection is feasible. Benign adenomas of the ampulla should be removed



Figure 6. EUS Showing Hypoechoic, Heterogeneous Mass at the Ampulla Limited to the Superficial and **Deep Mucosal Layers**

entirely by endoscopic ampullectomy. Conversely, malignant or invasive lesions should be removed surgically, often requiring a pancreaticoduodenectomy for complete resection. Patients with ampullary carcinomas typically present with obstructive jaundice or pancreatitis (Washington 2010; Haghighi et al., 2012).

Classification according to the 7th Edition of the AJCC staging system for tumors of the ampulla of Vater is as follows: "Tis corresponds to carcinoma in situ, T1 tumors are limited to the ampulla of Vater or sphincter of Oddi, T2 tumors invade the duodenal wall, T3 tumors invade the pancreas, and T4 tumors invade peri-pancreatic soft tissues or other adjacent organs or structures other than the pancreas" (Young et al., 2010).

The ampulla appears as a hypoechoic structure in the wall of the duodenum regularly ranging from 8 to 12 mm. Ampullary tumors are hypoechoic masses at the ampulla which produce interface loss between different duodenal wall echogenic layers. The sphincter of Oddi may be difficult to visualize but would appear as a thin hypoechoic layer surrounding the pancreaticobiliary duct. Ito et al. (2007) reported "that extension of the hypoechoic mass within the biliary or pancreatic duct lumen, or wall thickening of the duct, suggests ductal infiltration" (Figure 6).

Nodal metastases are best evaluated by EUS. Chen et al. (2009) reported that "EUS was superior to CT and was equivalent to MRI for tumor detection and T and N staging of ampullary tumors. They reported that the accuracy in T staging for ampullary carcinomas was 72.7% for EUS, 53.8% for MRI, and 26.1% for CT (p<0.01 for EUS versus CT; p > 0.05 for EUS versus MRI. The accuracy in N staging for ampullary carcinomas was 66.7% for EUS, 76.9% for MRI, and 43.5% for CT with no statistically significant difference between the 3 modalities. Moreover, neither indwelling stents nor tumor size, differentiation, or endoscopic appearance affected the staging accuracy of EUS". Another report by Ito et al. (2010) showed "the overall diagnostic accuracy of EUS in ampullary tumor staging ranged from 62 and 90%. Decreased accuracy and under staging has been reported when a biliary stent is present".

CT is superior for detection of distant metastases. The technique for malignant lymph node detection

Newly diagnosed without treatment

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involves scanning the peri-pancreatic regions for any suspicious nodes. According to classification of the 7th Edition of the AJCC "regional lymph nodes (N1) are peri-pancreatic nodes including: hepatic, hepatic artery, omental, peri-portal, infra-pyloric, celiac, superior mesenteric, retroperitoneal, and lateral aortic (lumbar) nodes. Tumor involvement of other nodal groups such as splenic and para-aortic lymph nodes and those at the tail of the pancreas are not regional and classified as distant metastases (M1). FNA can be performed of any malignant appearing lymph nodes for cytological analysis" (Edge and Compton 2010).

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