GRUPUGE Recommendations
ENDOSCOPIC ULTRASOUND IN ONCOLOGY

2019

LIST OF AUTHORS

Ana Caldeira
Department of Gastroenterology
Hospital Amato Lusitano, Castelo Branco, Portugal

Ana Luísa Santos
Department of Gastroenterology
Centro Hospitalar e Universitário São João, Porto, Portugal

Joana Carvão
Department of Gastroenterology
Hospital Central do Funchal, Madeira, Portugal

Miguel Bispo
Department of Gastroenterology and Digestive Endoscopy
Champalimaud Foundation, Lisboa, Portugal

Nuno Nunes
Department of Gastroenterology
Hospital do Divino Espírito Santo de Ponta Delgada, Açores, Portugal

Richard Azevedo
Department of Gastroenterology
Hospital Amato Lusitano, Castelo Branco, Portugal

Sílvia Leite
Department of Gastroenterology
Hospital Senhora da Oliveira, Guimarães, Portugal

Susana Lopes
Department of Gastroenterology
Centro Hospitalar e Universitário São João, Porto, Portugal

Teresa Moreira
Department of Gastroenterology
Centro Hospitalar do Porto, Porto, Portugal

Acknowledgments

The authors wish to acknowledge the valuable contribution of
Dr. Rosa Coelho in the construction and edition of these Recommendations.

LIST OF ABREVIATIONS

BE	Barrett Esophagus
CA	Celiac Axis
CC	Cholangiocarcinoma
CED-EUS	Contrast-Enhanced Doppler Endoscopic Ultrasound
CE-EUS	Contrast-Enhanced Endoscopic Ultrasound
CEH-EUS	Contrast-Enhanced Harmonic Endoscopic Ultrasound
CHA	Common Hepatic Artery
CPN	Celiac Plexus Neurolysis
CRC	Colorectal Cancer
CRM	Circumferential Resection Margin
CRT	Chemoradiotherapy
CT	Computed Tomography
EAC	Esophageal Adenocarcinoma
EAUS	Endoanal Ultrasound
EBUS	Endobronchial Ultrasound
EC	Esophageal Cancer
EGJ	Esophagogastric Junction
ER	Endoscopic Resection
ERCP	Endoscopic Retrograde Cholangiopancreatography
ESMO	European Society for Medical Oncology
EUS	Endoscopic Ultrasound
EUS-BD	Endoscopic Ultrasound Guided Biliary Drainage
EUS-CPN	Endoscopic Ultrasound Guided Celiac Plexus Neurolysis
EUS-E	EUS-Elastography
FISH	Fluorescence in situ hybridization
FNA	Fine Needle Aspiration
FNB	Fine Needle Biopsy
FNI	Fine Needle Injection
G	Gauge
GIST	Gastrointestinal Stromal Tumor
HF-EUS	High-Frequency Endoscopic Ultrasound
IDUS	Intraductal Ultrasonography
IVC	Inferior Vena Cava
LAPC	Locally Advanced Pancreatic Cancer
LN	Lymph Node
MDCT	Multidetector Computed Tomography
MI	Mechanical Index
MRCP	Magnetic Resonance Cholangiopancreatography
MRF	Mesorectal Fascia
MRI	Magnetic Resonance Imaging
NCCN	National Comprehensive Cancer Network
nCRT	Neoadjuvant Chemoradiotherapy
NPV	Negative Predictive Value
NSCLC	Non-Small Cell Lung Cancer
PET	Positron Emission Tomography
PDAC	Pancreatic Ductal Adenocarcinoma
P-NET	Pancreatic Neuroendocrine Tumor
POC	Peroral Cholangioscopy

PPV	Positive Predictive Value
PTBD	Percutaneous Transhepatic Biliary Drainage
PV	Portal Vein
ROI	Region of Interest
ROSE	Rapid On-Site Cytopathologist Evaluation
S	Sensitivity
SCC	Squamous Cell Carcinoma
SE	Strain Elastography
SH	Strain Histogram
SMA	Superior Mesenteric Artery
SMV	Superior Mesenteric Vein
SOC	Standard of Care
Sp	Specificity
TEM	Transanal Endoscopic Microsurgery
TIC	Time-Intensity Curve
TME	Total Mesorectal Excision
TNM	Tumor, Node, Metastasis
UCA	Ultrasonographic Contrast Agent

TABLE OF CONTENTS

1

Esophageal Cancer

Teresa Moreira

KEY POINTS

- The inclusion of EUS in esophageal cancer staging protocols has proved beneficial in patient management and is cost-effective.
- EUS should be performed in patients being considered for surgery after M1 disease has been excluded.
- Routine EUS staging of patients with Barrett esophagus before endoscopic resection is not recommended as future clinical decision making will rest on the endoscopic resection histological findings.
- The role of EUS in staging of early esophageal cancer is limited, having potential benefit in lesions with suspicious features for submucosal invasion or lymph node metastasis for which endoscopic therapy is being considered.
- The accuracy in identifying malignant lymph nodes is increased with the addition of EUS-FNA, with implications in the definition of the radiation field.
- Obstructing tumors not traversable by a gastroscope should be considered locally advanced and EUS may not add any additional information.
- EUS is not routinely used for restaging after neoadjuvant therapy due to its relatively low accuracy and tendency to overstage the disease.
- In patients with signs or symptoms suspicious of recurrence, EUS with FNA should be performed to establish a diagnosis.

Introduction

Approximately 75% of patients with esophageal cancer (EC) present with advanced tumors at diagnosis, 80% with metastatic lymph nodes and 50% with distant metastasis. The prognosis is highly related to disease stage (survival at 5 years in localized disease of 45% and of 5% in distant disease [1]), making staging essential for establishing the prognosis. Accurate staging is also mandatory for selecting the appropriate treatment options, not only to select patients for neoadjuvant chemoradiotherapy (nCRT) or endoscopic resection (ER), but also to minimize the rate of unnecessary surgery in metastatic disease.

Harewood *et al.* [2] evaluated the impact of endoscopic ultrasound (EUS) in EC staging, demonstrating a reduction of 42.1% in mortality and improvement in the recurrence-free survival rate, compared to patients without EUS evaluation. The incorporation of CT, positron emission tomography (PET) and EUS in preoperative staging reduced the number of unnecessary surgeries from 44% to 21% [3].

Staging

The TNM classification by the American Joint Committee on Cancer (AJCC) is the most accepted staging classification and is based on the analysis of local tumor invasion (T), lymph node involvement (N) and distant metastasis (M) [4] – Table 1.

Since the 7th edition (2010), the AJCC anatomic stage/prognostic groups for EC differ depending on histologic type, taking in consideration the different biology and mortality rate between esophageal adenocarcinoma (EAC) and squamous cell carcinoma (SCC). Nevertheless, the TNM components for staging EAC and SCC are identical. The first step in EC staging should be to exclude distant metastasis, and a PET-CT or a contrast-enhanced CT scan of the chest and abdomen is recommended, distinguishing M0 vs. M1 stages. EUS for locoregional staging should be performed if there is no evidence of M1 disease, as it has proved to be the most accurate method for locoregional staging. A number of studies have demonstrated EUS to be superior to CT scan, magnetic resonance imaging (MRI), or PET scanning with an overall accuracy of EUS for T and N staging of 90% [5]. Sihvo and coworkers found EUS to be more accurate in detecting locoregional lymph node metastasis than PET and CT (72%, 60%, and 58%, respectively) [6]. A retrospective study of 148 patients [7] found that PET was not as accurate as EUS-guided fine needle aspiration (EUS-FNA) and PET did not alter nodal staging in any patient with complete EUS-FNA. A study evaluating EUS, CT, and PET in staging EC found that EUS changed management by guiding the need for neoadjuvant therapy in 34.8% of patients [8]. The major impact on treatment plans of EUS was in patients with locally advanced disease: EUS identified a significantly greater number of patients (58.9%) with locoregional nodes than either CT (26.8%, p=0.0006) or PET (37.5%, p=0.02) [8]. In a prospective study of 75 patients with EC, PET scan, CT, and EUS were performed with tissue confirmation or FNA used as the “gold standard” of disease [9]. Accurate T stage by CT and PET was seen in 42% of cases and by EUS in 71% (p=0.14). CT, EUS, and PET had a similar performance in nodal staging [9].

The role of EUS in T staging

EUS provides detailed examination of the esophageal wall and currently is the procedure of choice for determining clinical T stage. Dedicated echoendoscopes using frequencies of 7.5 and 12 MHz visualize the esophageal wall as a five-layered structure - first hyperechoic layer: superficial mucosa; second hypoechoic layer: deep mucosa; third hyperechoic layer: submucosa; fourth hypoechoic layer: muscularis propria and fifth hyperechoic layer: adventitia. High frequency endoscopic ultrasound (HF-EUS) miniprobes, using frequencies of 12-20 MHz provide a more detailed visualization, permitting delineation of seven or nine layers in the esophageal wall.

Tumors appear as a hypoechoic expansion, and the degree of infiltration of the tumor through the esophageal wall layers determines the tumor stage. The mucosal layer includes the epithelium, lamina propria, and muscularis mucosae and is separated from the submucosa by a basement membrane. According to a meta-analysis by Puli *et al.* [5], including 49 studies (n = 2558), EUS sensitivity and specificity for T stage was 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 staging, respectively.

Early EC are those that are classified as Tis (high-grade dysplasia, which includes noninvasive neoplastic epithelial, previously carcinoma *in situ*) or T1 cancers, further divided into T1a and T1b subcategories. T1a cancers are confined to the mucosa and are often called intramucosal cancers, they can invade the lamina propria, as deeply as the muscularis mucosae, T1b cancers invade the submucosa, T2 cancers invade the muscularis propria, T3 cancers invade the adventitia, and T4 cancers correlates with invasion of adjacent structures such as the pleura, diaphragm, pericardium, azygos vein, or peritoneum (T4a disease), and the trachea, aorta, lungs, or heart (T4b disease) [4].

Early esophageal cancer and Barrett esophagus

Lesions limited to the mucosa (T1a) have a low risk of lymph node metastasis (3-10%) and can be treated effectively with ER, while invasion into the submucosa (T1b) increases the risk of lymph node metastasis to 16%-23% [10,11] requiring surgical resection, although “low-risk” T1b can be defined after ER and surgery avoided in selected patients.

The role of EUS for T staging of early EC has been a matter of debate, as some of the available data had shown controversial results. In the meta-analysis by Puli *et al.* [5], the accuracy was higher for T3-T4 lesions (>90%) than T1-T2 (65%), and the meta-analysis by Young *et al.* [12] (12 studies) concluded that EUS is not sufficiently accurate (67%) in determining the T-stage of high-grade dysplasia or superficial adenocarcinoma when compared with pathology specimens obtained by ER or surgery. Although, a more recent meta-analysis by Thosani *et al.* [13] including 19 studies (n=1019) with only superficial EC, reported a EUS sensitivity and specificity of 85% and 87% for T1a and 86% and 86% for T1b respectively, with an overall accuracy for superficial EC staging of more than 93%.

Nonetheless, the limited value of EUS in early EC has been supported by several other studies. One retrospective study included 131 patients with early EC [14]; in 10 of the 26 patients with EUS suggestive of submucosal invasion and/or lymph node metastasis, the ER specimen did not confirm the results, and 25 of the 105 patients with normal EUS findings had ER specimens with risk factors for lymph node metastasis, showing that EUS alone is not sufficient to exclude a patient

from endoscopic treatment and reinforcing the role of diagnostic ER. A recent retrospective study [15], including 335 patients with Barrett esophagus (BE) showed that overstaging occurred in 7% of patients, and EUS selected 11% for incorrect treatment modalities compared with pathologic staging.

The role of HF-EUS in early EC was also evaluated. A prospective study by Pech *et al.* [16], compared the accuracy of HF-EUS and conventional EUS in distinguishing between mucosal and submucosal adenocarcinoma arising in BE; the accuracy of HF-EUS was significantly higher than radial EUS (64% vs. 49%), however, the overall accuracy was unsatisfactory with both techniques. Another study [17] including 106 patients with both SCC and EAC in BE found that HF-EUS had limited accuracy in the detection of submucosal invasion. Overall, accuracy to differentiate T1a from T1b tumors was 73.5% and incorrect staging occurred in 26.5% (overstaging 18.6%, understaging 7.8%). A recent meta-analysis [18] comparing EUS with magnification endoscopy plus NBI (ME-NBI) in the evaluation of SCC, included 10 studies (n=1033), and demonstrated that ME-NBI was superior to white light endoscopy and had a similar diagnostic accuracy compared with HF-EUS in the evaluation of invasion depth.

In conclusion, EUS has a limited role in the staging of early EC prior to endoscopic or surgical treatment and it has a suboptimal accuracy to warrant its routine inclusion in the work-up of these patients. A meticulous endoscopic evaluation with subsequent ER is the best method for determining depth of invasion (T staging). The main role for EUS in this setting is to exclude lymph nodes involvement in “high-risk” lesions with suspicious features for submucosal invasion or lymph node metastasis, performing EUS-FNA if necessary.

The role of EUS in N staging

Esophageal cancer has a high rate of early lymph node involvement [10,11]. Lymph node metastasis are the main prognostic factor and survival depends largely on the number of positive nodes detected. Since the 7th edition AJCC, the N stage relates to the number of involved lymph nodes, rather than their location, being N1 (1-2), N2 (3-6), and N3 (≥7).

Besides the important role predicting the prognosis, N staging is also critical to define a treatment plan, as the detection of N positive disease is an indication for neoadjuvant treatment.

A meta-analysis by Puli *et al.* [5], reported a sensitivity of EUS for N staging of 85% and showed that the use of FNA substantially improved the sensitivity and specificity of EUS nodal staging from 85% to 97% and 85% to 96% respectively, with a low rate of complications, ranging from 0% to 2.3%.

EUS is used to evaluate size, shape, border and sonographic characteristics of regional lymph nodes. Several nodal characteristics are associated with malignant involvement: larger (>10 mm), more rounded, well demarcated border, hypoechoic lymph nodes are most likely to contain metastasis. The presence of all four features has a sensitivity of 89% and specificity of 92% for malignancy. However, reliance only on EUS imaging assessment has limitations, because only 25% of the metastatic lymph nodes will show all these criteria [19]. Vazquez-Sequeiros and coworkers [20] proposed the modified lymph node criteria for EC staging, with the addition of three EUS features: lymph node in the celiac region, ≥5 nodes identified, and T3-T4 disease. These modified EUS criteria showed improved accuracy compared to standard criteria (86% when ≥3 of the 7 modified EUS criteria were present).

In a study by Eloubeidi *et al.* [21], the identification of a celiac lymph node was synonymous to LN metastasis in 90% of the cases regardless of echo features and size, indicating a poor prognosis.

EUS-FNA

Tissue confirmation of nodal involvement or metastatic disease is important for selecting appropriate treatment. Peri-esophageal lymph nodes can only be approached by FNA when they are not located immediately adjacent to the primary tumor, given the high risk of contamination and seeding.

The addition of FNA to EUS improves detection of malignant lymph nodes. In a multicenter study of 171 patients, EUS-FNA of 192 lymph nodes was performed [22], reporting a sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for N staging of 92%, 93%, 100%, and 86%, respectively. Another study comparing lymph node staging using EUS alone vs. EUS-FNA [23], showed that EUS-FNA was associated with significantly better sensitivity (63% vs. 93%) and accuracy (70% vs. 93%). In a prospective study by Chen *et al*. [24], EUS-FNA demonstrated a sensitivity of 98.3%, specificity of 100% and was more accurate compared to lymph node echo-features alone (99.4% vs. 75.4%, $p<0.001$). These results were supported by a prospective study that compared the performance characteristics of CT, EUS, and EUS FNA in preoperative lymph node staging of EC in 125 patients [25] The accuracy of EUS FNA for lymph node staging (87%) was higher than that of EUS alone (74%, $p=0.01$) or helical CT (51%, $p<0.001$). Treatment plan was also impacted by performing FNA on suspicious lymph nodes [25]. In a more recent meta-analysis, EUS-FNA was 92% sensitive and 93% specific for N staging, with a PPV of 100% and a NPV of 86% [26]. Another study revealed an accuracy of 94% for EUS-FNA of celiac lymph node metastasis [27].

An additional benefit from confirming or excluding nodal involvement by EUS is that it will help calculate the exact radiation field, especially when the lymph node is away from the primary tumor, thus minimizing radiation induced complications [28].

Limitations

The accuracy of EUS is operator-dependent. The available evidence suggests that interobserver agreement is influenced by experience and tumor stage.

Among expert endosonographers (more than 75 exams) [29], overstaging was reported in 8 to 14%, more frequently in T2 tumors, which can be attributed to peritumoral inflammation. Understaging has been reported in 3 to 15%, often associated with T3 tumors with microscopic infiltration of the adventitia, beyond the resolution of the currently available equipments.

The accuracy of EUS for staging EC is lower in tumors larger than 5 cm with T overstaging in 36.4% and N in 31.8%, and in esophagogastric junction (EGJ) tumors [30]. A study found that EUS accuracy at the EGJ was inferior to that of other regions of the esophagus with 23% under-staged and 29% over-staged by EUS. The negative effect was particularly pronounced with smaller, early EGJ cancers being more frequently overstaged [31].

Routine staging with endoscopic ultrasound in patients with obstructing EC and dysphagia rarely impacts treatment decisions. A 2016 multicentric study showed that the inability to advance a

diagnostic gastroscope through a malignant stricture correlates with locally advanced disease on 100% of cases [32]. In another study, 67.1% patients had a partially or completely obstructing mass on initial endoscopy, of which 136 (93.8%) were locally advanced ($p<0.0001$ vs. non-obstructing lesions) [33].

Restaging after neoadjuvant therapy

The accuracy of EUS is limited after neoadjuvant chemoradiotherapy. EUS poorly differentiates tumor from necrosis or inflammatory reaction leading to overestimation of the depth of tumoral invasion and potentially incorrectly excluding patients from surgical resection.

A meta-analysis [34] on the staging accuracy of EUS for EC after nCRT, involving 16 studies (n= 724), showed a pooled sensitivity and specificity of EUS to diagnose T1 stage tumor of 23% and 95%, for T2 stage of 29% and 84%, for T3 stage of 81% and 42%, T4 stage of 43% and specificity of 96% respectively. In determining N stage, the pooled sensitivity and specificity of EUS were 69% and 52%. Tumors restaged by EUS as T4 should not be assigned to surgery because they are very likely inoperable. EUS is not reliable for N staging with its poor sensitivity and specificity. Subgroup analysis showed that staging accuracy did not improve with operator experience [34].

Another meta-analysis [35] on endoscopic biopsy and EUS for the detection of pathologic complete response after nCRT in EC demonstrated that although EUS after nCRT yields a high sensitivity, only a limited number of patients will have negative findings at EUS with still a substantial false-negative rate. Furthermore, EUS provides only moderate accuracy for detecting residual lymph node involvement. Based on these findings, these endoscopic modalities are not reliable for restaging after nCRT [35].

EUS should only be performed in specific cases after neoadjuvant therapy, such as FNA of a suspicious lymph node that would change management [28].

Detecting locoregional recurrence

In patients who present with alert symptoms or signs for locoregional recurrence and have a negative endoscopic and radiographic evaluation, EUS proved to be extremely accurate for detecting locoregional relapse, with a sensitivity and specificity over 90%, and it should be considered in the evaluation of those patients [36]. Also, surveillance by EUS of resected patients, showed a high PPV of tumor recurrence (92%), with two-thirds of the patients with recurrence still asymptomatic. Nevertheless it was not possible to demonstrate that early detection of recurrence improves survival [37].

Table 1. TNM criteria for esophageal cancer by the American Joint Committee on Cancer (8th edition) [4].

Category		Criteria
T category	**T0**	No evidence of primary tumor
	Tis	High-grade dysplasia, defined as malignant cells confined by the basement membrane
	T1	Tumor invades the lamina propria, muscularis mucosae, or submucosa
	T1a	Tumor invades the lamina propria or muscularis mucosae
	T1b	Tumor invades the submucosa
	T2	Tumor invades the muscularis propria
	T3	Tumor invades adventitia
	T4	Tumor invades adjacent structures
	T4a	Tumor invades the pleura, pericardium, azygos vein, diaphragm, or peritoneum
	T4b	Tumor invades other adjacent structures, such as aorta, vertebral body or trachea
	TX	Tumor cannot be assessed
N category	**NX**	Regional lymph nodes cannot be assessed
	N0	No regional lymph node metastasis
	N1	Metastasis in 1–2 regional lymph nodes
	N2	Metastasis in 3–6 regional lymph nodes
	N3	Metastasis in 7 or more regional lymph nodes
M category	**M0**	No distant metastasis
	M1	Distant metastasis
Adenocarcinoma G category	**GX**	Differentiation cannot be assessed
	G1	Well differentiated. >95% of tumor is composed of well-formed glands
	G2	Moderately differentiated. 50% to 95% of tumor shows gland formation
	G3†	Poorly differentiated. Tumors composed of nest and sheets of cells with <50% of tumor demonstrating glandular formation
Squamous cell carcinoma G category	**GX**	Differentiation cannot be assessed
	G1	Well-differentiated. Prominent keratinization with pearl formation and a minor component of nonkeratinizing basal-like cells. Tumor cells are arranged in sheets, and mitotic counts are low
	G2	Moderately differentiated. Variable histologic features, ranging from parakeratotic to poorly keratinizing lesions. Generally, pearl formation is absent
	G3‡	Poorly differentiated. Consists predominantly of basal-like cells forming large and small nests with frequent central necrosis. The nests consist of sheets or pavement-like arrangements of tumor cells, and occasionally are punctuated by small numbers of parakeratotic or keratinizing cells
Squamous cell carcinoma L category#	**LX**	Location unknown
	Upper	Cervical esophagus to lower border of azygos vein
	Middle	Lower border of azygos vein to lower border of inferior pulmonary vein
	Lower	Lower border of inferior pulmonary vein to stomach, including esophagogastric junction

†: If further testing of "undifferentiated" cancers reveals a glandular component, categorize as adenocarcinoma G3
‡: If further testing of "undifferentiated" cancers reveals a squamous cell component, or if after further testing they remain undifferentiated, categorize as squamous cell carcinoma G3.
#: Location is defined by epicenter of esophageal tumor.

References

1. Noone AM, Howlader N, Krapcho M, Miller D, Brest A, Yu M, *et al.* SEER Cancer Statistics Review, 1975-2015, National Cancer Institute. Bethesda, MD. SEER Cancer Stat Rev 1975-2015, Natl Cancer Institute Bethesda, MD. 2018.
2. Harewood GC, Kumar KS. Assessment of clinical impact of endoscopic ultrasound on esophageal cancer. J Gastroenterol Hepatol. 2004 Apr;19(4):433-9.
3. van Westreenen HL, Heeren PAM, van Dullemen HM, van der Jagt EJ, Jager PL, Groen H, *et al.* Positron emission tomography with F-18-fluorodeoxyglucose in a combined staging strategy of esophageal cancer prevents unnecessary surgical explorations. J Gastrointest Surg. 2005 Jan;9(1):54-61.
4. Amin M, Edge SB, Greene FL, Byrd D, Brookland R, Washington M, *et al.* AJCC Cancer Staging Manual, 8th edition. Springer. 2017.
5. Puli SR, Reddy J-B, Bechtold M-L, Antillon D, Ibdah J-A, Antillon M-R. Staging accuracy of esophageal cancer by endoscopic ultrasound: a meta-analysis and systematic review. World J Gastroenterol. 2008 Mar 14;14(10):1479-90.
6. Sihvo EIT, Rasanen J V, Knuuti MJ, Minn HRI, Luostarinen MES, Viljanen T, *et al.* Adenocarcinoma of the esophagus and the esophagogastric junction: positron emission tomography improves staging and prediction of survival in distant but not in locoregional disease. J Gastrointest Surg. 2004 Dec;8(8):988-96.
7. Keswani RN, Early DS, Edmundowicz SA, Meyers BF, Sharma A, Govindan R, *et al.* Routine positron emission tomography does not alter nodal staging in patients undergoing EUS-guided FNA for esophageal cancer. Gastrointest Endosc. 2009 Jun;69(7):1210-7.
8. Pfau PR, Perlman SB, Stanko P, Frick TJ, Gopal D V, Said A, *et al.* The role and clinical value of EUS in a multimodality esophageal carcinoma staging program with CT and positron emission tomography. Gastrointest Endosc. 2007 Mar;65(3):377-84.
9. Lowe VJ, Booya F, Fletcher JG, Nathan M, Jensen E, Mullan B, *et al.* Comparison of positron emission tomography, computed tomography, and endoscopic ultrasound in the initial staging of patients with esophageal cancer. Mol Imaging Biol. 2005 Nov-Dec;7(6):422-30.
10. Merkow RP, Bilimoria KY, Keswani RN, Chung J, Sherman KL, Knab LM, *et al.* Treatment trends, risk of lymph node metastasis, and outcomes for localized esophageal cancer. J Natl Cancer Inst. 2014 Jul 16;106(7).
11. Dubecz A, Kern M, Solymosi N, Schweigert M, Stein HJ. Predictors of lymph node metastasis in surgically resected T1 esophageal cancer. Ann Thorac Surg. 2015 Jun;99(6):1879-85; discussion 1886.
12. Young PE, Gentry AB, Acosta RD, Greenwald BD, Riddle M. Endoscopic Ultrasound Does Not Accurately Stage Early Adenocarcinoma or High-Grade Dysplasia of the Esophagus. Clin Gastroenterol Hepatol. 2010 Dec;8(12):1037-41.
13. Thosani N, Singh H, Kapadia A, Ochi N, Lee JH, Ajani J, *et al.* Diagnostic accuracy of EUS in differentiating mucosal versus submucosal invasion of superficial esophageal cancers: a systematic review and meta-analysis. Gastrointest Endosc. 2012 Feb;75(2):242-53.
14. Pouw RE, Heldoorn N, Herrero LA, Ten Kate FJW, Visser M, Busch OR, *et al.* Do we still need EUS in the workup of patients with early esophageal neoplasia? A retrospective analysis of 131 cases. Gastrointest Endosc. 2011 Apr;73(4):662-8.
15. Bartel MJ, Wallace TM, Gomez-Esquivel RD, Raimondo M, Wolfsen HC, Woodward TA, *et al.* Role of EUS in patients with suspected Barrett's esophagus with high-grade dysplasia or early esophageal adenocarcinoma: impact on endoscopic therapy. Gastrointest Endosc. 2017 Aug;86(2):292-298.
16. Pech O, Gunter E, Dusemund F, Ell C. Value of high-frequency miniprobes and conventional radial endoscopic ultrasound in the staging of early Barrett's carcinoma. Endoscopy. 2010 Feb;42(2):98-103.
17. Chemaly M, Scalone O, Durivage G, Napoleon B, Pujol B, Lefort C, *et al.* Miniprobe EUS in the pretherapeutic assessment of early esophageal neoplasia. Endoscopy. 2008 Jan;40(1):2-6.
18. Yu T, Geng J, Song W, Jiang Z. Diagnostic Accuracy of Magnifying Endoscopy with Narrow Band Imaging and Its Diagnostic Value for Invasion Depth Staging in Esophageal Squamous Cell Carcinoma: A Systematic Review and Meta-Analysis. Biomed Res Int. 2018 May 20;2018:8591387.
19. Catalano MF, Sivak M V., Rice T, Gragg LA, Van Dam J. Endosonographic features predictive of lymph node metastasis. Gastrointest Endosc. 1994 Jul-Aug;40(4):442-6.
20. Vazquez-Sequeiros E, Levy MJ, Clain JE, Schwartz DA, Harewood GC, Salomao D, *et al.* Routine vs. selective EUS-guided FNA approach for preoperative nodal staging of esophageal carcinoma. Gastrointest Endosc. 2006 Feb;63(2):204-11.

21. Eloubeidi MA, Wallace MB, Reed CE, Hadzijahic N, Lewin DN, Van Velse A, *et al.* The utility of EUS and EUS-guided fine needle aspiration in detecting celiac lymph node metastasis in patients with esophageal cancer: a single-center experience. Gastrointest Endosc. 2001 Dec;54(6):714-9.
22. Wiersema MJ, Vilmann P, Giovannini M, Chang KJ, Wiersema LM. Endosonography-guided fine-needle aspiration biopsy: diagnostic accuracy and complication assessment. Gastroenterology. 1997 Apr;112(4):1087-95.
23. Vazquez-Sequeiros E, Norton LD, Clain JE, Wang KK, Affi A, Allen M, *et al.* Impact of EUS-guided fine-needle aspiration on lymph node staging in patients with esophageal carcinoma. Gastrointest Endosc. 2001 Jun;53(7):751-7.
24. Chen VK, Eloubeidi MA. Endoscopic ultrasound-guided fine needle aspiration is superior to lymph node echofeatures: a prospective evaluation of mediastinal and peri-intestinal lymphadenopathy. Am J Gastroenterol. 2004 Apr;99(4):628-33.
25. Vazquez-Sequeiros E, Wiersema MJ, Clain JE, Norton ID, Levy MJ, Romero Y, *et al.* Impact of Lymph Node Staging on Therapy of Esophageal Carcinoma. Gastroenterology. 2003 Dec;125(6):1626-35.
26. van Vliet EPM, Heijenbrok-Kal MH, Hunink MGM, Kuipers EJ, Siersema PD. Staging investigations for oesophageal cancer: a meta-analysis. Br J Cancer. 2008 Feb 12;98(3):547-57.
27. Marsman WA, van Wissen M, Bergman JJ, van Lanschot JJ, Obertop H, Tytgat GN, *et al.* Outcome of patients with esophageal carcinoma and suspicious celiac lymph nodes as determined by endoscopic ultrasonography. Endoscopy. 2004 Nov;36(11):961-5.
28. DaVee T, Ajani JA, Lee JH. Is endoscopic ultrasound examination necessary in the management of esophageal cancer? World J Gastroenterol. 2017 Feb 7;23(5):751-762.
29. Fockens P, Van den Brande JHM, Van Dullemen HM, Van Lanschot JJB, Tytgat GNJ. Endosonographic T-staging of esophageal carcinoma: A learning curve. Gastrointest Endosc. 1996 Jul;44(1):58-62.
30. Heeren PA, van Westreenen HL, Geersing GJ, van Dullemen HM, Plukker JT. Influence of tumor characteristics on the accuracy of endoscopic ultrasonography in staging cancer of the esophagus and esophagogastric junction. Endoscopy. 2004 Nov;36(11):966-71.
31. Dhupar R, Rice RD, Correa AM, Weston BR, Bhutani MS, Maru DM, *et al*. Endoscopic ultrasound estimates for tumor depth at the gastroesophageal junction are inaccurate: Implications for the liberal use of endoscopic resection. Ann Thorac Surg. 2015 Nov;100(5):1812-6.
32. Bang JY, Ramesh J, Hasan M, Navaneethan U, Holt BA, Hawes R, *et al.* Endoscopic ultrasonography is not required for staging malignant esophageal strictures that preclude the passage of a diagnostic gastroscope. Dig Endosc. 2016 Sep;28(6):650-6.
33. Mansfield SA, El-Dika S, Krishna SG, Perry KA, Walker JP. Routine staging with endoscopic ultrasound in patients with obstructing esophageal cancer and dysphagia rarely impacts treatment decisions. Surg Endosc. 2017 Aug;31(8):3227-3233.
34. Sun F, Chen T, Han J, Ye P, Hu J. Staging accuracy of endoscopic ultrasound for esophageal cancer after neoadjuvant chemotherapy: a meta-analysis and systematic review. Dis Esophagus. 2015 Nov-Dec;28(8):757-71.
35. van Rossum PSN, Goense L, Meziani J, Reitsma JB, Siersema PD, Vleggaar FP, *et al.* Endoscopic biopsy and EUS for the detection of pathologic complete response after neoadjuvant chemoradiotherapy in esophageal cancer: a systematic review and meta-analysis. Gastrointest Endosc. 2016 May;83(5):866-79.
36. Catalano MF, Sivak M V., Rice TW, Van Dam J. Postoperative screening for anastomotic recurrence of esophageal carcinoma by endoscopic ultrasonography. Gastrointest Endosc. 1995 Dec;42(6):540-4.
37. Fockens P, Manshanden CG, Van Lanschot JJB, Obertop H, Tytgat GNJ. Prospective study on the value of endosonographic follow-up after surgery for esophageal carcinoma. Gastrointest Endosc. 1997 Dec;46(6):487-91.

2

Lung Cancer

Miguel Bispo

KEY POINTS

- In patients with known or suspected potentially resectable lung cancer whose imaging reveals mediastinal lymphadenopathy, EUS-FNA should be performed to document advanced disease (N+).
- In patients with paratracheal lymphadenopathy endobronchial ultrasound-FNA should be performed if it adds information to the staging.
- In patients with known or suspected potentially resectable lung cancer whose imaging shows no evidence of lymphadenopathy, combined EUS-FNA and endobronchial ultrasound-FNA should be performed for staging.
- In nodal staging, all parts of lymph nodes should be sampled (centre and edge) and, in the absence of ROSE, 3 needle passes should be performed.
- Suction should not be used for EUS-FNA of lymph nodes and the routine use of a stylet is discouraged.
- ROSE should be considered for EUS-FNA in centers in which specimen adequacy rates are below 90%.
- For EUS-core biopsy, ROSE has no significant impact on the overall accuracy.

Introduction

Lung cancer is the leading cause of cancer-related mortality in the western countries [1]. It is histologically divided into 2 main types: small cell lung cancer, which comprises about 15% of cases, and non-small cell lung cancer (NSCLC), which comprises the majority of cases (85%) [2].

For patients with small cell lung cancer, systemic chemotherapy is an important component of treatment, because this subtype is disseminated at presentation in almost all patients [2]. Non-small cell lung cancer is staged according to the TNM system, which features the characteristics of the local tumor (T), the presence or absence of regional lymph nodes metastases (N) and the presence or absence of distant metastases (M) [3]. Accurate staging of NSCLC is mandatory for allocation to surgical treatment, which is curative only in cases of localized disease. In general, surgical treatment cannot be recommended in patients with T4, N2–N3 disease (lymph nodes metastasis in subcarinal or contralateral mediastinal lymph nodes), or M1-disease - the recommended treatment for these patients is chemotherapy and radiation therapy.

Endoscopic ultrasound (EUS) can be useful to assess each component of the TNM staging system [4,5]:

1. It can identify tumor invasion of mediastinal structures (T4), such as the left atrium, aorta, pulmonary vessels, vertebra and oesophagus.
2. It can detect and sample suspicious mediastinal lymph nodes found by computed tomography (CT) or by positron emission tomography (PET). Documentation of subcarinal (N2) or contralateral (N3) lymph nodes metastasis precludes surgery.
3. It can also identify and sample distant metastases to the celiac lymph nodes, left lobe of the liver, left adrenal gland and occasionally right adrenal gland (M1), which also precludes curative surgery.

In a prospective study in patients with NSCLC in the absence of mediastinal lymphadenopathy on CT, EUS-FNA impacted the management of 25% of patients and detected advanced disease that precluded surgery (T4, N2-3 or M1) in 12% [6].

Staging approach by EUS

Current guidelines suggest that EUS could be used as first-line approach both for diagnosis and for staging of suspected and proven lung cancer since it has a high accuracy for demonstrating lymph node metastases [4, 5]. Endoscopic ultrasound is useful in staging NSCLC when mediastinal lymphadenopathy is present on CT/PET-CT (to confirm N+) and also plays a significant role in identifying patients with unresectable disease (N2/N3) when lymphadenopathy is not present on CT/PET-CT imaging [6].

Mediastinal stations accessible by EUS

In patients with known or suspected potentially resectable lung cancer whose imaging reveals paraesophageal, posterior and inferior mediastinal lymphadenopathy, EUS-FNA should be performed [4,5].

Endoscopic ultrasound can easily identify and sample lymph nodes in the posterior and inferior mediastinum, a common site of lung metastases, inaccessible to most alternative staging modalities. Mediastinal lymph node stations are represented in figure 1. Stations 4L, 7, 8 and 9 are readily approachable by EUS and eventually stations 2L and 5, if lymph nodes are large enough [7]. EUS-FNA of station 6 has been described, but requires transaortic passage of the needle [8].

Anterior upper mediastinal nodes and intrapulmonary nodes are inaccessible to EUS-FNA and in both situations endobronchial ultrasound-

guided fine needle aspiration (EBUS-FNA) is the adequate sampling technique [7].

Lymph nodes with round shape, sharp margins and a short axis greater than 8.3 mm are more likely to be malignant and therefore EUS-FNA is recommended [9]. A recent study in Portugal documented a high prevalence of large mediastinal lymph nodes in comparison to Northern Europe, which may negatively influence the specificity for malignancy of nodal staging without FNA [10].

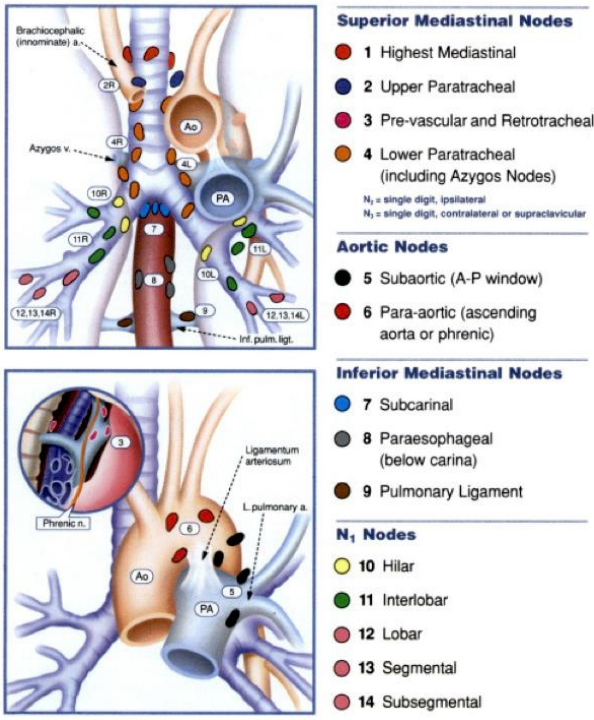

Figure 1.
Mediastinal lymph node stations approachable by EUS and EBUS. Stations 4L, 7, 8 and 9 are readily approachable by EUS and eventually stations 2L and 5. EBUS-FNA can access stations 1, 2, 4, 7, 10, 11, and 12. Ao, aorta; PA, pulmonary artery.
Reprinted from Mountain and Dresler [16], with permission.

Confirmation of malignancy in mediastinal lymph nodes by FNA is mandatory before excluding these patients from a potential curative surgery [7].

Even in the absence of suspicious lymph nodes on TC and/or PET-CT, EUS-FNA may identify mediastinal lymph nodes metastasis in up to 20% of patients [5]. This technique is often complemented with EBUS-FNA to access the entire mediastinum, because EUS-FNA is better to approach the posterior and inferior lymph nodes, while EBUS-FNA is better to approach the anterior and superior lymph nodes. EUS-FNA accuracy to identify metastases to mediastinal lymph nodes is high (83-97%), with a sensitivity of approximately 90% and specificity near 100% (false-positive rate of 2%) [5,11].

In general, negative findings by EUS-FNA or EBUS-FNA should be confirmed by surgical techniques (mediastinoscopy) [4,5].

Rapid advances in understanding the molecular pathogenesis of NSCLC have demonstrated that NSCLC is a heterogeneous group of diseases. Although the initial treatment of localized disease is the same, the molecular characterization of tumor tissue serves as a guide to treatment for patients with advanced disease (N+, M1). EUS-FNA aspirates of lymph nodes can be submitted to specific mutational analysis (such as for EGFR and K-ras mutations) to help tailor chemotherapy [12]. Restaging after neoadjuvant therapy can also be assessed by EUS-FNA to detect residual NSCLC [13].

Technical aspects of EUS-FNA in lung cancer staging

Very few studies have assessed the performance characteristics between 19G, 22G and 25G needles to perform EUS-FNA of lymph nodes, so there are no recommendations regarding the best needle to be used [14].

Diagnostic accuracy of EUS-FNA does not differ depending on whether the sampling is performed from the edge of a lymph node or from its centre [15]. All parts of lymph nodes should be sampled using a fanning technique (centre and edge) and 3

needle passes should be performed in the absence of rapid on-site cytopathologist evaluation (ROSE) [7].

There is some evidence that applying continuous suction with a syringe during EUS-FNA can slightly improve the sensitivity for the diagnosis of malignancy in solid masses but not in lymphadenopathy. In fact, EUS-FNA of lymphadenopathy showed that the use of suction has no impact on specimen quality and diagnostic yield and is associated with excessive bloodiness [14,15]. The wet suction EUS-FNA technique is a new modality for sampling shown to be superior to the standard EUS-FNA technique with suction (in terms of specimen quality and diagnostic yield) in solid pancreatic masses [15]. However, this technique has not yet been studied for sampling mediastinal lymph nodes in lung cancer staging.

Using the needle stylet does not seem to impact EUS-FNA sample quality and overall accuracy and is in fact associated with more bloodiness and increased procedure time and risk of accidental needle stick injuries [14].

The diagnostic yield of EUS-FNA with ROSE exceeds 90% [14,15]. For EUS-core biopsy, ROSE has no significant impact on the overall accuracy [15].

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018 Nov;68(6):394-424.
2. Bironzo P, Di Maio M. A review of guidelines for lung cancer. J Thorac Dis. 2018 May;10 (Suppl 13): S1556-S1563.
3. Amin MB, Edge S, Greene FL, Byrd DR, Brookland RK, Washington MK. AJCC cancer staging manual 8th ed. NewYork (NY): Springer-Verlag; 2017.
4. De Leyn P, Dooms C, Kuzdzal J, Lardinois D, Passlick B, Rami-Porta R, *et al*. Revised ESTS guidelines for preoperative mediastinal lymph node staging for non-small-cell lung cancer. Eur J Cardiothorac Surg. 2014 May;45(5):787-98.
5. Detterbeck FC, Postmus PE, Tanoue LT. The stage classification of lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2013 May;143(5 Suppl): e191S-e210S.
6. LeBlanc JK, Devereaux BM, Imperiale TF, Kesler K, DeWitt JM, Cummings O, *et al.* Endoscopic ultrasound in non-small cell lung cancer and negative mediastinum on computed tomography. Am J Respir Crit Care Med. 2005 Jan 15;171(2):177-82.
7. Jue TL, Sharaf RN, Appalaneni V, Anderson MA, Ben-Menachem T, Decker GA, *et al*. ASGE Standards of Practice Committee. Role of EUS for the evaluation of mediastinal adenopathy. Gastrointest Endosc. 2011 Aug;74(2):239-45.
8. von Bartheld MB, Rabe KF, Annema JT. Transaortic EUS-guided FNA in the diagnosis of lung tumors and lymph nodes. Gastrointest Endosc. 2009 Feb;69(2):345-9.
9. Chen VK, Eloubeidi MA. Endoscopic ultrasound-guided fine needle aspiration is superior to lymph node echofeatures: a prospective evaluation of mediastinal and peri-intestinal lymphadenopathy. Am J Gastroenterol. 2004 Apr;99(4):628-33.
10. Carmo J, Bispo M, Marques S, Chagas C. Prevalence and echo features of mediastinal lymph nodes in EUS for non-malignant indications: a prospective study in a Southern European Population. Endosc Int Open. 2018 Apr;6(4):E432-E436.
11. Annema JT, Versteegh MI, Veseliç M, Welker L, Mauad T, Sont JK*, et al.* Endoscopic ultrasound added to mediastinoscopy for preoperative staging of patients with lung cancer. JAMA. 2005 Aug 24;294(8):931-6.
12. Ulivi P, Romagnoli M, Chiadini E, Casoni GL, Capelli L, Gurioli C*, et al.* Assessment of EGFR and K-ras mutations in fixed and fresh specimens from transesophageal ultrasound-guided fine needle aspiration in non-small cell lung cancer patients. Int J Oncol. 2012 Jul;41(1):147-52.
13. Annema JT, Veseliç M, Versteegh MI, Willems LN, Rabe KF. Mediastinal restaging: EUS-FNA offers a new perspective. Lung Cancer. 2003 Dec;42(3):311-8.
14. Wani S, Muthusamy VR, Komanduri S. EUS-guided tissue acquisition: an evidence-based approach (with videos). Gastrointest Endosc. 2014 Dec;80(6):939-59.e7.
15. Polkowski M, Larghi A, Weynand B, Boustière C, Giovannini M, Pujol B, *et al*. European Society of Gastrointestinal Endoscopy (ESGE). Learning, techniques, and complications of endoscopic ultrasound (EUS)-guided sampling in gastroenterology: European Society of Gastrointestinal Endoscopy (ESGE) Technical Guideline. Endoscopy. 2012 Feb;44(2):190-206.
16. Mountain CF, Dresler CM. Regional lymph node classification for lung cancer staging. Chest. 1997 Jun;111(6):1718-23.

3

Gastric Cancer

Ana Luísa Lopes, Joana Carvão, Nuno Nunes

KEY POINTS

- EUS is recommended for preoperative staging of gastric cancer if metastatic disease is not evident on CT/PET-CT.
- EUS is the best non-surgical tool in evaluating the depth of invasion of primary gastric cancers, with a more accurate prediction of T and N stage than CT imaging.
- The most relevant data in gastric cancer staging is differentiating T1–T2 from T3–T4, and detecting lymph node (N) metastasis, which are better accomplished with EUS than with CT/PET-CT.
- EUS is not recommended for restaging after neo-adjuvant therapy.

Introduction

Gastric cancer remains the third leading cause of cancer-related deaths worldwide, despite decrease in incidence and mortality [1].

Although radical surgery is the mainstay of curative treatment, new modalities are gaining importance in the therapeutic approach of these patients, such as endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD) in early cancer with favourable prognosis features. Moreover, neo-adjuvant chemotherapy is recommended for patients with intermediate or advanced gastric cancer (>T1N0) [2]. Therefore an accurate pre-treatment clinical staging, with evaluation of tumor extent and nodal involvement is imperative and has significant implications in the therapeutic approach [3]. The 5-year survival rate ranges between 70% for early gastric cancer confined to the mucosa or submucosa (stage IA) and 4% in the presence of distant metastatic disease (stage IV) [4].

Different diagnostic tools can be used for diagnostic and staging of gastric cancer, including computed tomography (CT), magnetic resonance imaging (MRI) and positron emission tomography (PET). However they lack accuracy for assessing the depth of tumor invasion or lymph node involvement [5,6]. Endoscopic ultrasound (EUS) has emerged as the most reliable nonsurgical method in evaluating the depth of invasion of primary gastric cancers, with a superior prediction of T and N stage than CT imaging [7]. EUS also has a potential role detection of distant metastasis missed by CT (such as low-volume malignant ascites or small metastasis in the left liver lobe).

EUS for staging of gastric cancer

T staging

EUS is a very important procedure for local staging in patients with gastric cancer with a higher ability to study the gastric wall layers (T stage).

The overall accuracy of EUS in determining T stage ranges from 71 and 92%. [8,9] Moreover, a meta-analyse of 50 studies reported a higher sensitivity and specificity of EUS in discriminating early to intermediate (T1-T2) vs. advanced (T3-T4) gastric carcinomas [0.86 (95% CI 0.81 to 0.90) and 0.90 (95% CI 0.87 to 0.93)] [2,8]. Some studies reported a better performance in the diagnosis of advanced tumors than early ones, in which the specificity was poor [8]. The diagnostic accuracy was lower for gastric lesions <30 mm when compared with lesions ≥30 mm [10].

Some studies reported a difficulty in differentiating T2 from T3 invasion, leading to potential under-staging and over-staging. Whereas microscopic invasion was the most frequent cause of under-staging, over-staging was attributed to peri-tumoral fibrosis, ulceration, and inflammation [6].

However the performance of EUS in detection of mucosal and submucosal invasion of early gastric cancer (T1a vs. T1b) is relatively low, even with the use of high frequency miniprobes. A meta-analysis, with data from 16 studies, showed a pooled sensitivity and specificity for mucosal staging of 76% (95% CI, 74–78%) and 72% (95% CI, 69–75%), and for submucosal staging of 62% (95% CI, 59–66%) and 78% (95% CI, 76– 80%), respectively [11]. So, as previously suggested, EUS is not considered good enough, with no significant advantage over conventional endoscopy by an expert endoscopist for early gastric cancer staging.

Nodal staging

Nodal staging is essential for gastric cancer staging. Even though no formal recommendations exist, a systematic approach for evaluation of perigastric and regional lymph node stations has been described by Sharma *et al.* [12].

Large size hypoechoic lymph nodes with sharp borders and round shape are highly suggestive of malignant involvement [13].

According to a recent Cochrane meta-analysis that included 44 studies with 3573 patients and in which EUS was compared with pathology evaluation, EUS showed an overall sensitivity and specificity of 0.83 (95% CI 0.79 to 0.87) and 0.67 (95% CI 0.61 to 0.72), respectively for nodal staging [2]. So, EUS performance is lower in diagnosing lymph node status (positive vs. negative), such as for diagnosing superficial tumors (T1a vs. T1b), compared to overall T-stage accuracy.

In a comparison study of CT scan and EUS with postoperative pathology reports, EUS demonstrated greater accuracy for N0 and N1 (N0, 75.7% vs. 61.1%; N1, 58.6% vs. 48.5%; p=0.003 and 0.044), lower accuracy for N2 (27.8% vs. 38.9%, p=0.046) and similar accuracy for N3 staging (6.0% vs. 8.4%, p=0.549) when compared to CT scan [14]. In a comparative study of 256 patients, EUS outperformed PET-CT scan in nodal staging with an overall accuracy of 76.2% vs. 72.5% (p=0.02), respectively.

EUS accuracy for nodal staging is limited for several reasons. First, there is a difficult distinction between malignant and inflammatory lymph nodes. Secondly, EUS is less accurate in detecting distant lymph nodes. Also, EUS is operator-dependent and an inter-observer variability has been described (κ values of 0.46, 0.34 and 0.34 for N0, N1 and N2 stages, respectively) [15]. Despite these limitations, EUS evaluation is recommend by the National Comprehensive Cancer Network (NCCN) guidelines if metastatic cancer is not evident [16].

EUS-fine needle aspiration (FNA), improves the accuracy of EUS for nodal staging, however interposition of the tumor often limits FNA of perilesional lymph nodes.

Metastatic staging

EUS may provide useful information regarding M staging due to the accessibility of the left hepatic lobe, peritoneum, pleura and mediastinum. In a meta-analysis, EUS had an overall polled sensitivity for the diagnosis of distant metastasis of 73.2% (95% CI: 63.2-81.7) [9]. The addition of FNA for suspected metastatic lymph nodes or lesions can preclude unnecessary surgery in up to 15 % of cases [17]. EUS has been shown to be more sensitive than other imaging modalities in the detection of ascites, with a sensitivity of 90% reported in some studies; the presence of ascites correlates well with the depth of tumor invasion and lymph node metastases. Moreover, the performance of a EUS paracentesis may help in the diagnostic of peritoneal carcinomatosis, with a positive predictive value of 75% [6,18]. It is important to observe the mediastinum, because metastasis in distant nodes can be seen, and confirmed by FNA. In a study involving 242 patients 42% had positive EUS-guided FNA, when targeting distant metastasis, based on echo features and location. Most sampled lesions were mediastinum nodes [17,19].

EUS for gastric cancer restaging after neo-adjuvant therapy

EUS offers little value in restaging, with prognostic impact only in patients in whom downstaging was observed. So EUS is not recommended in this setting [8].

Table 1. TNM criteria for gastric cancer by the American Joint Committee on Cancer (8th edition) [4].

Category		Criteria
T category	**TX**	Primary tumor cannot be assessed
	T0	No evidence of primary tumor
	Tis	Carcinoma in situ: intraepithelial tumor without invasion of the lamina propria
	T1	Tumor invades lamina propria, muscularis mucosae, or submucosa
	T1a	Tumor invades lamina propria or muscularis mucosae
	T1b	Tumor invades submucosa
	T2	Tumor invades muscularis propria
	T3	Tumor penetrates subserosal connective tissue without invasion of visceral peritoneum or adjacent structures
	T4	Tumor invades serosa (visceral peritoneum) or adjacent structures
	T4a	Tumor invades serosa (visceral peritoneum)
	T4b	Tumor invades adjacent structures
N category	**NX**	Regional lymph node(s) cannot be assessed
	N0	No regional lymph node metastasis
	N1	Metastasis in 1-2 regional lymph nodes
	N2	Metastasis in 3-6 regional lymph nodes
	N3	Metastasis in seven or more regional lymph nodes
	N3a	Metastasis in 7-15 regional lymph nodes
	N3b	Metastasis in 16 or more regional lymph nodes
M category	**M0**	No distant metastasis
	M1	Distant metastasis

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018 Nov;68(6):394-424.
2. Simone M, Sandro P. Diagnostic accuracy of endoscopic ultrasonography (EUS) for the preoperative locoregional staging of primary gastric cancer. Cochrane Database Syst. Rev. 2015.
3. Merkow RP, Herrera G, Goldman DA, Gerdes H, Schattner MA, Markowitz AJ, *et al*. Endoscopic Ultrasound as a Pretreatment Clinical Staging Tool for Gastric Cancer: Association with Pathology and Outcome. Ann Surg Oncol. 2017 Nov;24(12):3658-3666.
4. American Joint Committee on Cancer. Digestive System. Amin MB, Edge S, Greene F, Byrd DR, Brookland RK, *et al*, eds. AJCC Cancer Staging Manual. 8th edition. New York, NY: Springer. 2016.
5. Botet JF, Lightdale CJ, Zauber AG, Gerdes H, Winawer SJ, Urmacher C, *et al*. Preoperative staging of gastric cancer: comparison of endoscopic US and dynamic CT. Radiology. 1991 Nov;181(2):426-32.
6. Holt B, Rosch T, Peter S. EUS in the Evaluation of Gastric Tumors, in: R. Hawkes, P. Fockens, S. Varadarajulu (Eds.), Endosonography, 3rd ed., Elsevier, Philadelphia, 2015: 398.
7. Blackshaw G, Lewis WG, Hopper AN, Morgan MA, Al-Khyatt W, Edwards P, *et al*. Prospective comparison of endosonography, computed tomography, and histopathological stage of junctional oesophagogastric cancer. Clin Radiol. 2008 Oct;63(10):1092-8.
8. Redondo-Cerezo E, Martínez-Cara JG, Jiménez-Rosales R, Valverde-López F, Caballero-Mateos A, Jérvez-Puente P, *et al*. Endoscopic ultrasound in gastric cancer staging before and after neoadjuvant chemotherapy. A comparison with PET-CT in a clinical series. United European Gastroenterol J. 2017 Aug;5(5):641-647.
9. Puli SR, Bechtold ML, Buxbaum JL, Eloubeidi MA. How Good Is Endoscopic Ultrasound–Guided Fine-Needle Aspiration in Diagnosing the Correct Etiology for a Solid Pancreatic Mass? Pancreas. 2013 Jan;42(1):20-6.
10. Okada K, Fujisaki J, Kasuga A, Omae M, Yoshimoto K. Hirasawa, *et al*. Endoscopic ultrasonography is valuable for identifying early gastric cancers meeting expanded-indication criteria for endoscopic submucosal dissection. Surg. Endosc. 2011 Mar;25(3):841–848.
11. Pei Q, Wang L, Pan J, Ling T., Zou X. Endoscopic ultrasonography for staging depth of invasion in early gastric cancer: A meta-analysis. J Gastroenterol Hepatol 2015 Nov;30(11): 1566–1573.
12. Sharma M, Rai P, Rameshbabu C. Techniques of imaging of nodal stations of gastric cancer by endoscopic ultrasound. Endosc. Ultrasound. 2014 Jul;3(3):179-90.
13. Evans, Chandrasekhara V, Chathadi KV, Decker GA, Early DS, Fisher DA, *et al*. The role of endoscopy in the management of premalignant and malignant conditions of the stomach. Gastrointest Endosc. 2015 Jul;82(1):1–8.
14. Kwee RM, Kwee TC. Imaging in assessing lymph node status in gastric cancer, Gastric Cancer. 2009 Apr;12(1):6–22.
15. Meining A, Dittler HJ, Wolf A, Lorenz R, Schusdziarra V, Siewert JR, *et al*. You get what you expect? A critical appraisal of imaging methodology in endosonographic cancer staging. Gut. 2002 May;50(5):599–603.
16. Ajani JA, D'Amico TA, Almhanna K, Bentrem DJ, Chao J, Das P, *et al.* Gastric Cancer, Version 3.2016. NCCN Clinical Practice Guidelines in Oncology. J. Natl. Compr. Cancer Netw. 2016 Oct;14(10): 1286–1312.
17. Hassan H, Vilmann P, Sharma V. Impact of EUS-guided FNA on management of gastric carcinoma. Gastrointest Endosc. 2010 Mar;71(3):500-4.
18. Sharma V, Rana SS, Ahmed SU, Guleria S, Sharma R, Gupta R. Endoscopic ultrasound-guided fine-needle aspiration from ascites and peritoneal nodules: A scoping review. Endosc Ultrasound. 2017 Nov-Dec;6(6):382-388.
19. Puli S, Batapati Krishna Reddy J, Bechtold M, Antillon MR, Ibdah JA. How good is endoscopic ultrasound for TNM staging of gastric cancers? A meta-analysis and systematic review. World J Gastroenterol. 2008 Jul;14(25):4011–4019.

4

Pancreatic Cancer

Joana Carvão, Susana Lopes

KEY POINTS

- EUS is particularly valuable in the detection of small pancreatic lesions (<2 cm) specially if previously undetected by CT or MRI.
- EUS-FNA is clearly recommended in patients where neoadjuvant or palliative chemotherapy is indicated. The role in resectable cancer is still debatable.
- EUS has a higher sensitivity than CT scan for nodal staging and portal vein confluence invasion with similar specificity. CT has a higher sensitivity and specificity than EUS for arterial (superior mesenteric artery and celiac trunk) invasion.
- EUS false negatives may occur in the setting of chronic pancreatitis, diffusely infiltrating carcinoma, exuberant ventral/dorsal splits and a recent episode of acute pancreatitis.
- EUS-guided fine needle injection has the potential to deliver therapeutic agents in locally advanced pancreatic cancer allowing direct therapy with higher concentrations and low systemic side effects.
- EUS-guided biliary drainage is an alternative to percutaneous or surgical drainage in patients in whom ERCP has failed.
- Endoscopic ultrasound-guided celiac plexus neurolysis is an alternative in pain management in unresectable pancreatic cancer.

Introduction

In Europe, there are approximately 100,000 new cases of pancreatic cancer every year [1]. Pancreatic cancer has the lowest survival rate of all cancers and a life expectancy of just 4,6 months [2].

The low survival rates are mostly due to the difficulty in the early diagnosis with only 9.7% of all pancreatic cancers being diagnosed at a local stage, where resection may be applicable [3].

Endoscopic ultrasonography (EUS) has gained an emerging role in the management of pancreatic ductal adenocarcinoma. In this review we will discuss the contribution of EUS in the detection, diagnosis, staging and therapeutic applications in pancreatic cancer.

EUS applications in detection, diagnosis and staging of pancreatic cancer

Detection

EUS is the most sensitive imaging test for the detection of pancreatic lesions with a reported overall sensitivity of 87-100% [4]. EUS superiority over conventional computed tomography has been previously reported in the literature [5–7]. Similarly, EUS has higher sensitivity against multidetector computed tomography scans (MDCT), with a reported sensitivity of 98-100% compared to 86%, respectively [8,9].

When compared to magnetic resonance imaging (MRI), the data is scarce and conflicting with regard to EUS superiority [10,11].

EUS greatest benefit over computed tomography scan (CT) and MRI is for the detection of small pancreatic neoplasms (less than 2-3 cm) that were previously undetected with these imaging methods, with sensitivity of 87-93% compared with 53% for MDCT and 67% for MRI [10,12].

However, EUS may not be able to identify pancreatic neoplasms, even by the most experience endosonographers, in patients with chronic pancreatitis, diffusely infiltrating carcinomas, ventral/dorsal splits, recent episode of acute pancreatitis, and therefore an alternative imaging method or follow-up EUS is advised [13].

New image-based technologies such as contrast-enhanced endoscopic ultrasonography (CE-EUS) and elastography may add additional information when differentiating pancreatic cancer from other lesions. In CE-EUS, a second-generation low mechanical index microbubble ultrasound agent is injected into a peripheral vein of the patient providing real time perfusion imaging [3]. Pancreatic adenocarcinomas show hypo-enhancement while neuroendocrine tumors and pseudotumoral chronic pancreatitis show hyper- or iso-enhancement, respectively [14]. In fact, a hypo-echoic, hypo-enhancing lesion is highly sensitive (>86%) for adenocarcinoma while a hyper-enhancing lesion is highly specific (over 98%) to exclude adenocarcinoma [15]. Recently, in a systematic review, the pooled sensitivity and specificity of CE-EUS in the diagnosis of pancreatic carcinoma was considered very high [16]. However, CE-EUS is still not part of standard practice due to the high cost and lack of expertise.

In EUS elastography tissue elasticity is measured in real time, both in a qualitative (based on colour pattern) and a quantitative (based on a strain ratio or histogram) form. Hard tissues are shown in dark blue, intermediate hardness in green, medium soft tissue in yellow and soft tissue in red [17]. There are no clear stiffness *cut-off* values for pancreatic masses, however in a prospective study by Iglesias-Garcia *et al.*, high strain ratio (>10) or low strain histogram (<50), had a high probability of malignancy [18].

The overall sensitivity and specificity of EUS elastography in solid pancreatic masses was 93% and 63%, respectively [19]. Limitations of this technique include interobserver variability and the presence of motion artefacts.

Diagnosis

EUS greatest advantage is the ability to obtain tissue samples by fine needle aspiration (FNA). Three of the largest meta-analysis on the diagnostic accuracy of EUS-FNA in solid pancreatic lesions have demonstrated a sensitivity of 85-92% and a specificity of 94-100% [20–22].

EUS-FNA in pancreatic cancer is clearly recommended in patients where neoadjuvant or palliative chemotherapy is indicated and is not mandatory in patients with potentially resectable lesions (negative predictive value 60-70%) [23,24] However, this last point is a matter of discussion. [18] With the advent of the possibility of criteria expansion for neoadjuvant chemotherapy in resectable cancers and the subclassification of pancreatic cancer into subtypes for personalized therapy, FNA may be generalized, in the future to all pancreatic cancers [25,26].

EUS-FNA is associated with a low rate of complications (0.82%), mainly mild pancreatitis. [27] Tumor seeding has been described rarely in case reports [4].

Several FNA needles are available ranging from 19 to 25 gauge (G). 25-G needle has been associated with higher sensitivity but comparable specificity to the 22-G needle in solid pancreatic lesions [28]. 25-G needle may also have an advantage in fibrotic lesions and those located in head or uncinated process of the pancreas [17]. Also different techniques for sampling have been described. The “fanning” technique has the advantage of requiring less tissue passages for histologic diagnosis [29]. The wet suction technique also improves cellularity and specimen adequacy [30].

The presence of an on-site pathologist – rapid on-site evaluation (ROSE) - has also shown to increase diagnostic sensitivity and overall accuracy for malignancy in observational studies. However these findings have not been reproduced in further randomized controlled trials and therefore is not currently a standard in clinical practice [31].

In order to improve the diagnostic yield of EUS-FNA in pancreatic masses, analysis of DNA markers in biopsy samples is being investigated. The most studied marker is K-ras, since 75-95% of all pancreatic cancer present this oncogene mutation. When EUS-FNA is combined with K-ras mutation analysis of the sample it can increase the diagnostic accuracy from 85% to 94% [32].

Finally, 19-G to 25-G fine-needle biopsy (FNB) needles have been introduced with the advantage of allowing core biopsies with preserved architecture for histological analysis. [3] Studies are controversial regarding the advantage over FNA. A recent meta-analysis did not reveal significant differences in diagnostic accuracy between FNA and FNB (86,2% and 85,8%, OR 0.88 p=0.53, respectively) [33].

Staging

Staging of pancreatic adenocarcinoma is based on the most current tumor, node, metastasis (TNM) system by the American Joint Committee on Cancer. Currently on the 8th edition, profound changes have been made on the tumor and node stages [34]. (Table 1).

Both National Comprehensive Cancer Network (NCCN) and European Society for Medical Oncology (ESMO) consider MDCT as a gold standard for staging. However, EUS is indicated for further assessment if initial MDCT does not reveal distant metastasis by ESMO, while NCCN suggest that EUS is complimentary to CT, primarily for cytological diagnosis [23,24].

EUS is an accurate technique for staging, as shown by a large meta-analysis of 1330 patients, where EUS had a higher sensitivity than CT scan for nodal staging (58% vs. 24%) and vascular invasion (86% vs. 58%) with similar specificity [35]. However, it should be noted that comparative studies for T-staging are limited due do the changes of TNM staging criteria over time.

Additionally, from a therapeutic point of view, pancreatic cancer should be further classified according to its resectability status into resectable, borderline resectable (or locally advanced) and unresectable [17]. Resectability status depends mainly on vascular invasion [23]. (Table 2). EUS criteria to predict vascular invasion are: 1. peri-pancreatic venous collaterals in an area of a mass that obliterates the normal anatomic location of a major portal confluence vessel; 2. tumor within the vessel lumen; 3. abnormal vessel contour with loss of the vessel-parenchymal sonographic interface [36].

A recent meta-analysis found EUS to be 0.87 sensitive and 0.80 specific for identifying unresectable disease in patient who were believed to have resectable pancreatic adenocarcinoma after a CT scan was performed [37]. These findings were further corroborated in a systematic review that found preoperative EUS evaluation to be associated with an increased identification of unresectable disease patients with pancreatic adenocarcinoma (identified unresectable disease in 19% of patients with 95% confidence interval, 10±33%, after CT scan) [38].

Therefore EUS has the potential to influence the surgical management by identifying patients with locally advanced disease who would not benefit from curative resection. It should also be highlighted the role of EUS in the characterization of atypical portocaval lymph nodes, ascitic fluid, peritoneal nodules and suspected liver metastasis.

Table 1. TNM criteria for pancreatic ductal adenocarcinoma by the American Joint Committee on Cancer (8^{th} edition) [34].

Category		Criteria
T category	**T1**	Maximum tumor diameter ≤2 cm
	T2	Maximum tumor diameter 2-4 cm
	T3	Maximum tumor diameter >4 cm
	T4	Tumor involves the celiac axis or the superior mesenteric artery
N category	**N0**	No regional lymph node metastasis
	N1	Metastasis in 1 – 3 regional lymph nodes
	N2	Metastasis in ≥4 regional lymph nodes
M category	**M0**	No distant metastasis
	M1	Distant metastasis

Table 2. Adapted criteria for resectability status of pancreatic ductal adenocarcinoma, according to NCC guidelines [23]

Vessel	Resectable	Borderline resectable	Unresectable
Portal Vein (PV)/Superior Mesenteric Vein (SMV)	No contact, <180º without vein contour irregularity	Contact >180º, <180º with deformity or vein thrombosis but allowing safe and complete resection and reconstruction, contact with inferior vena cava (IVC)	Unreconstructible obstruction, contact with most proximal draining jejunal branch
Common Hepatic Artery (CHA)	No arterial tumor contact	Contact without extension to CA or CHA bifurcation	Contact with extension to CA or CHA bifurcation
Celiac Axis (CA)	No arterial tumor contact	No contact (head), contact <180º (body and tail)	Contact >180º, any contact with aorta
Superior Mesenteric Artery (SMA)	No arterial tumor contact	Contact <180º	Contact >180º, contact with first jejunal SMA branch, contact with aorta

Therapeutic EUS applications in pancreatic cancer

Fine needle injection of biologic anti-tumor agents

EUS-guided fine needle injection (FNI) has the potential to deliver therapeutic agents in locally advanced pancreatic cancer (LAPC), allowing direct therapy with higher concentrations and low systemic side effects.

The first report of EUS-guided FNI was released in 2000 with a mixed lymphocyte culture of donor and host mononuclear cells (cytoimplant). In this small phase I trial of 8 patients, 2 patients had partial and 1 had a minor response with a median survival of 13.2 months with no adverse events [39]. TNFerade is an immunotherapeutic agent that delivers human TNF-alpha gene to cancer cells using a replication-deficient adenoviral vector. In a large randomized phase III trial of EUS-FNI or percutaneous transabdominal intratumoral injection of TNFerade plus standard of care (SOC) vs. SOC alone, that included 304 patients, there were no differences in median progression-free survival (6.8 months vs. 7 months HR 0.96, 95%CI 0.69-1,32 p=0.51, respectively) and equal side effects [40]. In addition, multivariate analysis showed that TNFerade injection by EUS approach, rather than percutaneous transabdominal approach was a risk factor for inferior progression free survival [40].

Immature dendritic cells, BC-819 (DNA plasmid with overexpression of H19) have also been described with EUS-FNI, in small studies (<10 patients) with low evidence [41,42].

Even though EUS-FNI shows promising results, there is insufficient evidence to include it as a therapeutic alternative in LAPC.

Fiducial placement

Fiducials are radiographic markers that are implanted at the tumor site as a reference point for radiation beams in stereotactic radiotherapy. Since its first description by Pishvaian *et al.* in 2006, several case series have been published with a combined experience over 180 patients of fiducial placement in LAPC [43,44]. While traditional fiducials require 19-G needles, newer coil designs can be deployed by 22-G needles [45]. Overall, the technical success rates exceed 90% without the need of fluoroscopy and with low adverse events (minor bleeding and fiducial migration) [46].

Current NCCN guidelines indicate that EUS-guided fiducial placement is preferred over CT-guided placement [23].

Recently, a feasibility study showed EUS-guided delivery of a new liquid form fiducial in pancreatic cancers. Liquid fiducials have fewer artefacts and can be delivered in just one single puncture requiring only needle repositioning [47].

Brachytherapy

Brachytherapy involves directed radioactive seed placement and subsequent exposure to gamma radiation, producing localized tissue injury and ablation. The radioactive seeds include iridium-192, palladium-103 and iodine-125, with the latter being used more frequently due to the longest half-life. This technique allows delivery of high-dose radiation and low systemic toxicity. The radioactive seeds are placed with a 19-gauge needle and the numbers of seeds needed estimated trough EUS assessment of tumor volume [48]. Two pilot studies have been published that assess the role of EUS-guided implantation of radioactive seeds in LAPC [49,50]. The first included 15 patients that were followed by a median 10.6 months, where 27% of patients had a "partial" tumor response, 20% showed a "minimal" response, and 33% demonstrated "stable disease". Clinical benefit was seen in almost a third of patients, mostly due to a reduction in pain [49]. In the second study that included 22 patients, all patients were implanted radioactive seeds followed by gemcitabine-based 5-fluorouracil chemotherapy, and overall there was an improvement in pain scores with no long-term survival benefit [50]. There were no major complications in both studies. Since then several studies have been published and a recent meta-analysis, that included 23 studies (824 patients), showed that brachytherapy alone was associated with 8.98 month overall survival-rate (95% CI 6.94-11.03) and relief of pain [51].

However, there are no randomized controlled data to support the use of EUS-guided brachytherapy as standard clinical practice.

EUS-guided biliary drainage

Obstructive jaundice due to tumor infiltration of the bile duct limits or even precludes the use of chemotherapy in neoadjuvant and palliative settings. Biliary drainage becomes, therefore, one of the cornerstones in the management of patients with pancreatic cancer [52].

EUS-guided biliary drainage (EUS-BD) was first described in 2001 by Giovannini *et al.* as a technique for biliary access when endoscopic retrograde cholangiopancreatography (ERCP) fails and as an alternative to surgical biliary bypass or percutaneous transhepatic biliary drainage (PTBD) [4,53]. ERCP may not be feasible due to altered anatomy, ampullary distortion, periampullary diverticulum, gastric outlet obstruction, tumor invasion or enteral stents [54]. EUS-BD can be broadly performed in two ways: direct transluminal stenting (hepatogastrostomy or choledochoenterostomy) or rendezvous technique (guide-wire placement in the intrahepatic or extrahepatic biliary duct trough the papilla and retrieved by a duodenoscope for biliary intervention) [4].

According to a recent systematic review and meta-analysis that evaluated the cumulative efficacy and safety of the transluminal approach of EUS-BD, a cumulative success rate of 90% and cumulative adverse events rate of 17% was noted [55]. Additionally, in the first systematic review and meta-analysis of the efficacy and safety of EUS-BD compared with PTBD in failed ERCP, that comprised 9 studies (of which 3 randomized controlled trials) with 483 patients, there was no significant difference in the technical success rate

between the two procedures. EUS-BD, however, was associated with less adverse events and re-intervention rates [56].

It should be highlighted that there are no randomized controlled trials to support the best strategy for EUS-BD, and therefore the approach should be decided on a case-to-case basis according to the biliary anatomy and condition.

Endoscopic ultrasound-guided celiac plexus neurolysis

Celiac plexus neurolysis (CPN) is a method for pain relief in pancreatic cancer by chemical destruction of the ganglia using dehydrated alcohol. Patients eligible for this procedure are patients with unresectable cancer and intractable pain. The timing of the procedure is extremely relevant due to the fact that as pancreatic cancer progresses, pain becomes less dependent on celiac plexus alone to involve other visceral and somatic nerves. In fact, one study showed that CPN was more effective when it was performed at an early stage after pain onset [57].

According to two meta-analysis, EUS-CPN alleviates abdominal pain in 73-80% of patients [58,59]. In addition, higher rates of pain management are seen when bilateral injection is applied [60]. When compared to conventional pain management, patients submitted to EUS-CPN had significantly higher rates of pain relief and less opioid consumption [61]. However, no difference between quality of life scores was noted.

Due to the inexistence of randomized trials of EUS vs. percutaneous approach a direct comparison of efficacy and safety between these techniques is not possible. Nevertheless, EUS-guided CPN performed for the palliation of pancreatic cancer pain appears to be as safe and effective as CPN performed by other techniques [60].

Conclusion

EUS and EUS-FNA are accurate techniques for the detection, diagnosis and staging of pancreatic cancer. EUS superiority over other imaging methods is mostly seen in small pancreatic lesions and the ability to acquire tissue samples. EUS has also gain an important therapeutic role, with the possibility to assist in the management of pancreatic cancer. However it remains unquestionable that the potential of diagnostic and therapeutic EUS varies among different centers depending on the local availability and operators expertise.

References

1. Rawlaa P, Sunkarab T, Gaduputic V, Epidemiology of Pancreatic Cancer: Global Trends, Etiology and Risk Factors, World J Oncol. 2019 Feb; 10(1): 10–27.
2. De Angelis R, Sant M, Coleman MP, Francisci S, Baili P, Pierannunzio D, *et al*. EUROCARE-5 Working Group. Cancer survival in Europe 1999–2007 by country and age: results of EUROCARE-5—a population-based study. Lancet Oncol. 2014 Jan;15(1):23-34.
3. Zhang L, Sanagapalli S, Stoita A. Challenges in diagnosis of pancreatic cancer. World J Gastroenterol. 2018 May 21;24(19):2047-2060.
4. Luz LP, Al-Haddad MA, Sey MSL, Dewitt JM. Applications of endoscopic ultrasound in pancreatic cancer. World J Gastroenterol. 2014 Jun 28;20(24):7808-18.
5. Gress FG, Hawes RH, Savides TJ, Ikenberry SO, Cummings O, Kopecky K, *et al*. Role of EUS in the preoperative staging of pancreatic cancer: a large single-center experience. Gastrointest Endosc. 1999 Dec;50(6):786-91.
6. Palazzo L, Roseau G, Gayet B, Vilgrain V, Belghiti J, Fékété F, *et al*. Endoscopic ultrasonography in the diagnosis and staging of pancreatic adenocarcinoma. Endoscopy. 1993 Feb;25(2):143-50.
7. Rösch T, Braig C, Gain T, Feuerbach S, Siewert JR, Schusdziarra V, *et al*. Staging of pancreatic and ampullary carcinoma by endoscopic ultrasonography: Comparison with conventional sonography, computed tomography, and angiography. Gastroenterology. 1992 Jan;102(1):188-99.
8. DeWitt J, Devereaux B, Chriswell M, McGreevy K, Howard T, Imperiale TF, *et al*. Comparison of endoscopic ultrasonography and multidetector computed tomography for detecting and staging pancreatic cancer. Ann Intern Med. 2004 Nov 16;141(10):753-63.
9. Agarwal B, Abu-Hamda E, Molke KL, Correa AM, Ho L. Endoscopic ultrasound-guided fine needle aspiration and multidetector spiral ct in the diagnosis of pancreatic cancer. Am J Gastroenterol. 2004 May;99(5):844-50.
10. Müller MF, Meyenberger C, Bertschinger P, Schaer R, Marincek B. Pancreatic tumors: evaluation with endoscopic US, CT, and MR imaging. Radiology. 1994 Mar;190(3):745-51.
11. Ainsworth A, Rafaelsen S, Wamberg P, Durup J, Pless T, Mortensen M. Is there a difference in diagnostic accuracy and clinical impact between endoscopic ultrasonography and magnetic resonance cholangiopancreatography? Endoscopy. 2003 Dec;35(12):1029-32.
12. Wang W, Shpaner A, Krishna SG, Ross WA, Bhutani MS, Tamm EP, *et al*. Use of EUS-FNA in diagnosing pancreatic neoplasm without a definitive mass on CT. Gastrointest Endosc. 2013 Jul;78(1):73-80.
13. Bhutani M, Gress F, Giovannini M, Erickson R, Catalano M, Chak A, *et al*. The no endosonographic detection of tumor (nest) study: a case series of pancreatic cancers missed on endoscopic ultrasonography. Endoscopy. 2004 May;36(5):385-9.
14. Kitano M, Yamashita Y. New Imaging Techniques for Endoscopic Ultrasonography. Gastrointest Endosc Clin N Am. 2017 Oct;27(4):569-583.
15. Fusaroli P, Spada A, Mancino MG, Caletti G. Contrast Harmonic Echo–Endoscopic Ultrasound Improves Accuracy in Diagnosis of Solid Pancreatic Masses. Clin Gastroenterol Hepatol. 2010 Jul;8(7):629-34.e1-2.
16. Fusaroli P, Napoleon B, Gincul R, Lefort C, Palazzo L, Palazzo M, *et al*. The clinical impact of ultrasound contrast agents in EUS: a systematic review according to the levels of evidence. Gastrointest Endosc. 2016 Oct;84(4):587-596.e10.
17. Gonçalves B, Soares JB, Bastos P. Endoscopic ultrasound in the diagnosis and staging of Pancreatic Cancer. GE Port J Gastroenterol. 2015 Jul 2;22(4):161-171.
18. Moutinho-Ribeiro P, Iglesias-Garcia J, Gaspar R, Macedo G. Early pancreatic cancer — The role of endoscopic ultrasound with or without tissue acquisition in diagnosis and staging. Dig Liver Dis. 2019 Jan;51(1):4-9.
19. Kitano M, Yoshida T, Itonaga M, Tamura T, Hatamaru K, Yamashita Y. Impact of endoscopic ultrasonography on diagnosis of pancreatic cancer. J Gastroenterol. 2019 Jan;54(1):19-32.
20. Puli SR, Bechtold ML, Buxbaum JL, Eloubeidi MA. How good is endoscopic ultrasound–guided fine-needle aspiration in diagnosing the correct etiology for a solid pancreatic mass? Pancreas. 2013 Jan;42(1):20-6.
21. Hewitt MJ, McPhail MJW, Possamai L, Dhar A, Vlavianos P, Monahan KJ. EUS-guided FNA for diagnosis of solid pancreatic neoplasms: a meta-analysis. Gastrointest Endosc. 2012 Feb;75(2):319-31.
22. Chen J, Yang R, Lu Y, Xia Y, Zhou H. Diagnostic accuracy of endoscopic ultrasound-guided fine-needle aspiration for solid pancreatic lesion: a systematic review. J Cancer Res Clin Oncol. 2012 Sep;138(9):1433-41.
23. Tempero MA, Malafa MP, Al-Hawary M, Asbun H, Bain A, Behrman SW, *et al*. Pancreatic adenocarcinoma, version 2.2017: Clinical practice guidelines in Oncology. JNCCN.J Natl Compr Canc Netw. 2017 Aug;15(8):1028-1061.
24. Ducreux M, Cuhna AS, Caramella C, Hollebecque A, Burtin P, Goéré D, *et al*. Cancer of the pancreas: ESMO

Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2015 Sep;26 Suppl 5:v56-68.
25. Van Tienhoven G, Versteijne E, Suker M, Groothuis KBC, Busch OR, Bonsing BA, *et al*. Preoperative chemoradiotherapy versus immediate surgery for resectable and borderline resectable pancreatic cancer (PREOPANC-1): A randomized, controlled, multicenter phase III trial. J Clin Oncol. 2018 Jun 20;36(18_suppl):LBA4002–LBA4002.
26. Aguirre AJ. Refining Classification of Pancreatic Cancer Subtypes to Improve Clinical Care. Gastroenterology. 2018 Dec;155(6):1689-1691.
27. Wang KX, Ben QW, Jin ZD, Du YQ, Zou DW, Liao Z, Li ZS. Assessment of morbidity and mortality associated with EUS-guided FNA: a systematic review. Gastrointest Endosc. 2011 Feb;73(2):283-90.
28. Madhoun M, Wani S, Rastogi A, Early D, Gaddam S, Tierney W, *et al*. The diagnostic accuracy of 22-gauge and 25-gauge needles in endoscopic ultrasound-guided fine needle aspiration of solid pancreatic lesions: a meta-analysis. Endoscopy. 2013;45(2):86-92.
29. Bang J, Magee S, Ramesh J, Trevino J, Varadarajulu S. Randomized trial comparing fanning with standard technique for endoscopic ultrasound-guided fine-needle aspiration of solid pancreatic mass lesions. Endoscopy. 2013 Jun;45(6):445-50.
30. Attam R, Arain MA, Bloechl SJ, Trikudanathan G, Munigala S, Bakman Y, *et al*. "Wet suction technique (WEST)": a novel way to enhance the quality of EUS-FNA aspirate. Results of a prospective, single-blind, randomized, controlled trial using a 22-gauge needle for EUS-FNA of solid lesions. Gastrointest Endosc. 2015;81(6):1401-7.
31. Marcin Polkowski A, Jenssen C, Kaye P, Carrara S, Deprez P, Gines A, *et al*. Technical aspects of EUS-guided sampling in gastroenterology: ESGE Technical Guideline-March. Endoscopy. 2017 Oct;49(10):989-1006.
32. Bournet B, Selves J, Grand D, Danjoux M, Hanoun N, Cordelier P, *et al*. Endoscopic ultrasound–guided fine-needle aspiration biopsy coupled with a kras mutation assay using allelic discrimination improves the diagnosis of pancreatic cancer. J Clin Gastroenterol. 2015 Jan;49(1):50-6.
33. Bang J, Hawes R, Varadarajulu S. A meta-analysis comparing ProCore and standard fine-needle aspiration needles for endoscopic ultrasound-guided tissue acquisition. Endoscopy. 2016 Apr;48(4):339-49.
34. S. Kakar, T. Pawlik, P. Allen, JN. Vauthey, Exocrine pancreas, in: A. MB (Ed.), AJCC Cancer Staging Man, 8th ed., Chicago, 2017: p. 337.
35. Nawaz H, Fan CY, Kloke J, Khalid A, McGrath K, Landsittel D, *et al*. Performance characteristics of endoscopic ultrasound in the staging of pancreatic cancer: a meta-analysis. JOP. 2013 Sep 10;14(5):484-97.
36. Snady H. EUS criteria for vascular invasion: analyzing the meta-analysis. Gastrointest Endosc. 2007 May;65(6):798-807.
37. Tamburrino D, Riviere D, Yaghoobi M, Davidson BR, Gurusamy KS. Diagnostic accuracy of different imaging modalities following computed tomography (CT) scanning for assessing the resectability with curative intent in pancreatic and periampullary cancer. Cochrane Database Syst Rev. 2016 Sep 15;9:CD011515.
38. James PD, Meng ZW, Zhang M, Belletrutti PJ, Mohamed R, Ghali W, *et al*. The incremental benefit of EUS for identifying unresectable disease among adults with pancreatic adenocarcinoma: A meta-analysis. PLoS One. 2017 Mar 20;12(3):e0173687.
39. Chang KJ, Nguyen PT, Thompson JA, Kurosaki TT, Casey LR, Leung EC, *et al*. Phase I clinical trial of allogeneic mixed lymphocyte culture (cytoimplant) delivered by endoscopic ultrasound-guided fine-needle injection in patients with advanced pancreatic carcinoma. Cancer. 2000 Mar 15;88(6):1325-35.
40. Herman JM, Wild AT, Wang H, Tran PT, Chang KJ, Taylor GE, *et al*. Randomized phase III multi-institutional study of TNFerade biologic with fluorouracil and radiotherapy for locally advanced pancreatic cancer: final results. J Clin Oncol. 2013 Mar 1;31(7):886-94.
41. Irisawa A, Takagi T, Kanazawa M, Ogata T, Sato Y, Takenoshita S, *et al*. Endoscopic ultrasound-guided fine-needle injection of immature dendritic cells into advanced pancreatic cancer refractory to gemcitabine. Pancreas. 2007 Aug;35(2):189-90.
42. Hanna N, Ohana P, Konikoff FM, Leichtmann G, Hubert A, Appelbaum L, et al. Phase 1/2a, dose-escalation, safety, pharmacokinetic and preliminary efficacy study of intratumoral administration of BC-819 in patients with unresectable pancreatic cancer. Cancer Gene Ther. 2012 Jun;19(6):374-81.
43. Pishvaian AC, Collins B, Gagnon G, Ahlawat S, Haddad NG. EUS-guided fiducial placement for CyberKnife radiotherapy of mediastinal and abdominal malignancies. Gastrointest Endosc. 2006 Sep;64(3):412-7.
44. Han J, Chang KJ. Endoscopic ultrasound-guided direct intervention for solid pancreatic tumors. Clin Endosc. 2017 Mar;50(2):126-137.
45. Khashab MA, Kim KJ, Tryggestad EJ, Wild AT, Roland T, Singh VK, *et al.* Comparative analysis of traditional and coiled fiducials implanted during EUS for pancreatic cancer patients receiving stereotactic body radiation therapy. Gastrointest Endosc. 2012 Nov;76(5):962-71.

46. Dhadham G, Hoffe S, Harris C, Klapman J. Endoscopic ultrasound-guided fiducial marker placement for image-guided radiation therapy without fluoroscopy: safety and technical feasibility. Endosc Int Open. 2016 Mar;4(3):E378-82.
47. Ussui V, Kuritzky N, Berzosa M. EUS -guided liquid fiducial placement for stereotactic radiotherapy in pancreatic cancer: Feasibility study. Endosc Ultrasound. 2018 Mar-Apr;7(2):135-136.
48. Mohan P, Seo DW. EUS-guided interventional management of pancreatic tumor. Gastrointest Interv. 2013. 1;2(1):17–23.
49. Sun S, Xu H, Xin J, Liu J, Guo Q, Li S. Endoscopic Ultrasound-Guided Interstitial Brachytherapy of Unresectable Pancreatic Cancer: Results of a Pilot Trial. Endoscopy. 2006 Apr;38(4):399-403.
50. Jin Z, Du Y, Li Z, Jiang Y, Chen J, Liu Y. Endoscopic ultrasonography-guided interstitial implantation of iodine 125-seeds combined with chemotherapy in the treatment of unresectable pancreatic carcinoma: a prospective pilot study. Endoscopy. 2008 Apr;40(4):314-20.
51. Han Q, Deng M, Lv Y, Dai G. Survival of patients with advanced pancreatic cancer after iodine125 seeds implantation brachytherapy: A meta-analysis. Medicine (Baltimore). 2017 Feb;96(5):e5719.
52. Domínguez-Muñoz JE, Lariño-Noia J, Iglesias-Garcia J. Biliary drainage in pancreatic cancer: The endoscopic retrograde cholangiopancreatography perspective. Endosc Ultrasound. 2017 Dec;6(Suppl 3):S119-S121.
53. Giovannini M, Moutardier V, Pesenti C, Bories E, Lelong B, Delpero J. Endoscopic Ultrasound-Guided Bilioduodenal Anastomosis: A New Technique for Biliary Drainage. Endoscopy. 2001 Oct;33(10):898-900.
54. Baars J, Kaffes A, Saxena P. EUS-guided biliary drainage: A comprehensive review of the literature. Endosc Ultrasound. 2018 Jan-Feb;7(1):4-9.
55. Khan MA, Akbar A, Baron TH, Khan S, Kocak M, Alastal Y, *et al.* Endoscopic Ultrasound-Guided Biliary Drainage: A Systematic Review and Meta-Analysis. Dig Dis Sci. 2016 Mar;61(3):684-703.
56. Sharaiha RZ, Khan MA, Kamal F, Tyberg A, Tombazzi CR, Ali B, *et al*. Efficacy and safety of EUS-guided biliary drainage in comparison with percutaneous biliary drainage when ERCP fails: a systematic review and meta-analysis. Gastrointest Endosc. 2017 May;85(5):904-914.
57. Ischia S, Ischia S, Polati E, Finco G. Three posterior percutaneous celiac plexus block techniques. A prospective, randomized study in 61 patients with pancreatic cancer pain. Anesthesiology. 1992 Apr;76(4):534-40.
58. Puli SR, Reddy JBK, Bechtold ML, Antillon MR, Brugge WR. EUS-Guided Celiac Plexus Neurolysis for Pain due to Chronic Pancreatitis or Pancreatic Cancer Pain: A Meta-Analysis and Systematic Review. Dig Dis Sci. 2009 Nov;54(11):2330-7.
59. Kaufman M, Singh G, Das S, Concha-Parra R, Erber J, Micames C, *et al.* Efficacy of endoscopic ultrasound-guided celiac plexus block and celiac plexus neurolysis for managing abdominal pain associated with chronic pancreatitis and pancreatic cancer. J Clin Gastroenterol. 2010 Feb;44(2):127-34.
60. Wyse JM, Battat R, Sun S, Saftoiu A, Siddiqui AA, Leong AT, *et al*. Practice guidelines for endoscopic ultrasound-guided celiac plexus neurolysis. Endosc Ultrasound. 2017 Nov-Dec;6(6):369-375.
61. Wyse JM, Carone M, Paquin SC, Usatii M, Sahai A V. Randomized, Double-Blind, Controlled Trial of Early Endoscopic Ultrasound–Guided Celiac Plexus Neurolysis to Prevent Pain Progression in Patients With Newly Diagnosed, Painful, Inoperable Pancreatic Cancer. J Clin Oncol. 2011 Sep 10;29(26):3541–6.

5

Bile Duct and Ampullary Cancer

Susana Lopes

KEY POINTS

- EUS is the most reliable modality for local preoperative staging of ampullary lesions, assessing the degree of intraductal tumor extension.
- EUS is better to differentiate between early (T1) and advanced (T2-4) tumors, being highly accurate in predicting endoscopic unresecability.
- If available, intraductal ultrasonography (IDUS) may help to stage early ampullary tumors, due to the possibility in delineating the sphincter of Oddi and duodenal submucosa.
- In patients with a CBD stricture of unknown etiology, EUS is the preferred diagnostic modality as it enables visualization of the entire CBD, regional lymphadenopathies, and tissue sampling by EUS-FNA.
- In patients with a proximal CBD stricture, EUS and EUS-FNA have several diagnostic limitations and the risk of needle track seeding, which may preclude liver transplantation. In these patients, ERCP-based tissue sampling should be considered as an alternative in addition to IDUS.
- IDUS presents the highest accuracy in differentiating benign from malignant CBD strictures.
- EUS and IDUS have proved superior to other imaging modalities in cholangiocarcinoma local staging, in detecting vascular invasion and determining resecability.
- EUS-FNA of lymph nodes should be performed in cholangiocarcinoma staging.
- Endoscopic ultrasound biliary drainage is a low-invasive, high successful, palliative treatment with an acceptably low rate of complications.

Ampullary tumors

Introduction

Ampullary tumors originate from the pancreatobiliary-duodenal junction, and although rare, they present a wide pathologic variety, being adenoma and carcinoma the more prevalent type. Adenomas are considered premalignant conditions, and precursors of carcinoma, in an adenoma-carcinoma sequence similar to colorectal cancer. Benign adenomas are increasingly being diagnosed in asymptomatic patients due to the generalization of upper endoscopy, and can occur sporadically or in the context of genetic syndromes such as familial adenomatous polyposis. The diagnosis of an ampullary tumor may be difficult, with a false negative pathological result in almost a third of patients due to intramural extension of the tumor. On the other hand, biopsies have been shown to underestimate the presence of adenocarcinoma in 19% to 30% of cases [1-5].

Staging

Endoscopic ampullectomy as replaced pancreato-duodenectomy in the treatment of patients with benign ampullary tumors or early cancer, due to its lower morbidity rate (6% to 36%) [6-9]. Nevertheless, careful selection is required to triage patients to the appropriate treatment approach as endoscopic ampullectomy is limited by its inability to assess for lymph node metastasis and resection of neoplastic tissue extending inside the pancreatic or bile ducts. These limitations highlight the importance of correct pretreatment staging, not only to assess the resectability of the tumor but also to determine which tumors may be best resected endoscopically or surgically.

Ampullary tumors are staged according to the TNM classification (Table1), and the presence of lymph node metastasis correlates with the T stage, ranging from 0% in T1a to 78% in T3-T4.

Endoscopic ultrasound (EUS) and intraductal ultrasonography (IDUS) can provide useful information in the evaluation of ampullary lesions, permitting assessment of the degree (if any) of intraductal extension of the tumor. EUS has been shown to be superior to Computed Tomography (CT), Magnetic Resonance Imaging (MRI), or transabdominal US for tumor staging [10-14]. Nevertheless, MRI performed better for nodal staging for these patients, whereas CT scans and Positron Emission Tomography (PET) scans can detect small metastases not seen on EUS or intraductal US. One prospective study comparing EUS, intraductal US, and CT scans found that tumor visualization was superior with intraductal US (100%) compared with EUS (59%) and CT (30%) [15]. More important is the accuracy of EUS in determining whether or not endoscopic resection can be used with curative intent. The accuracy of EUS in confirming that the T stage is higher than T1 is around 90% (ranging from 78% to 94%). EUS can therefore be considered to be highly accurate in predicting the unresectability of ampullary carcinoma and in determining the T stage. Nevertheless, EUS is limited by its inability to accurately demarcate the sphincter of Oddi, and its negative predictive value (NPV) for the presence of metastatic lymph nodes remains low. IDUS has been proposed as a more accurate ultrasonographic imaging tool for the staging of ampullary neoplasms. Intraductal catheter probes inserted via ERCP employ a higher frequency (20-MHz), resulting in enhanced resolution but with limited depth of penetration, resulting in inadequate N staging [16]. However, IDUS is probably the only imaging modality that can image the Oddi's muscle layer as a distinct layer. The possibility of delineating the sphincter of Oddi and the duodenal submucosa allows

superior T staging, particularly of early tumors that could be triaged to endoscopic therapy. In a series of 32 patients with ampullary cancer IDUS accuracy in showing intraductal involvement was 100% [17].

It is uncertain whether all patients with ampullary adenomas should undergo EUS before therapy. Some experts propose that lesions <1 cm in diameter or those that do not have obvious signs of malignancy (ulceration, induration, bleeding) do not require US evaluation before endoscopic removal [18]. In larger lesions or those with features suggestive of malignancy, EUS (and IDUS) should be performed before any decision about endoscopic vs. surgical treatment. If the tumor is staged above uT1 because of submucosal or muscularis propria invasion or present with intraductal infiltration, surgery is indicated. EUS evaluation should be done prior to any invasive intervention, as EUS interpretation will be compromised due to artifacts.

Bile duct cancer

Introduction

Biliary tract cancer is the second most common primary hepatobiliary malignancy after hepatocellular carcinoma. It encompasses gallbladder and bile duct tumors (cholangiocarcinoma-CC). Cholangiocarcinoma is best classified anatomically as intrahepatic and extrahepatic. Extrahepatic CC occurs anywhere within the extrahepatic bile duct, including the intrapancreatic portion and is further classified into hilar/perihilar (also called Klatskin tumor), or distal. Perihilar CC is the most common type of CC, followed by distal CC and then the intrahepatic forms. Cholangiocarcinomas can be further classified based on their macroscopic features as mass-forming, periductal-infiltrating (the most common), or intraductal tumors. For the purpose of this revision we will only focus on extrahepatic CC, a challenging disease in terms of both diagnosis and treatment. Despite its incidence appears to be declining, most patients present with unresectable disease at the time of diagnosis with dismal five-year survival rates.

The main sign in patients presenting with distal CC is painless jaundice, with only a minority presenting with cholangitis. When clinical and laboratory findings suggest biliary tract involvement, the first exam to perform is a transabdominal US. This image modality can reveal a dilated biliary tree, either intrahepatic with normal extrahepatic ducts, in which case a hilar CC is suspected or both intrahepatic and extrahepatic biliary dilation, suggesting a distal lesion [19]. The diagnosis and staging of extrahepatic CC involve a combination of different image modalities like magnetic resonance cholangiopancreatography (MRCP), CT scan (MDCT), endoscopic retrograde cholangiopancreatography (ERCP) and endoscopic US (EUS).

Diagnosis

Any biliary stricture should be considered malignant until proved otherwise, unless there is a past medical history very suggestive of a potential benign condition (ex: previous surgery).

MDCT identifies CCs in nearly 94% to 100% of patients, and the reported positive and negative predictive values to determine resectability are 92% and 85%, respectively [20-21]. MRCP with its ability to perform cholangiograms, permits definition of tumor location, anatomy and extent [22]. This non-invasive modality has an accuracy of up to 95% in tumor diagnosis [23].

Endoscopic evaluation, namely ERCP, is crucial in the diagnosis of bile duct malignancy. ERCP has the ability of being simultaneously a diagnostic and therapeutic procedure, allowing tissue sampling via brush cytology and endoscopic biopsy and biliary obstruction relief with stent placement. The diagnostic capability of ERCP-based tissue sampling is not very good. Although the specificity of brush cytology is 99%, its overall sensitivity is only 42%. In a study from Navaneethan *et al.*, the combination of brush cytology and intraductal biopsy only modestly increased the sensitivity to 59% and the specificity to 100%, suggesting that both methods combined only modestly increases the sensitivity [24]. Fluorescence in situ hybridization (FISH) uses fluorescently labeled DNA probes to identify chromosome abnormalities (polysomy or amplification). The addition of FISH can increase the sensitivity of detecting malignancy by 35-60% following a negative cytology [25]. A triple tissue sampling has been reported to have an overall sensitivity of 82% and specificity of 100% in the diagnosis of CC [26].

EUS has proved to be a useful tool in assessing biliary tract strictures/dilation because it readily enables visualization of the entire CBD and allows for tissue acquisition by EUS-FNA. In a systematic review published in 2016 [27], EUS-FNA proved to be sensitive and highly specific for diagnosing malignancy in biliary strictures, with a pooled sensitivity and specificity of 80% (95% CI, 74%-86%), and 97% (95% CI, 94%-99%) respectively. The pooled positive likelihood ratio was 12.35 (95% CI, 7.37-20.72), which essentially confirms malignancy, while a negative likelihood ratio of 0.26 (95% CI, 0.18-0.38) cannot reliably exclude malignancy. The pooled diagnostic odds ratio for diagnosing a malignant biliary stricture was 70.53 (95% CI, 38.62-128.82). One major limitation concerning EUS evaluation is its reported lower sensitivity for proximal biliary strictures and the concern for needle-tract seeding [28-30]. Needle-track seeding is less of a problem in distal lesions as the needle track of transduodenal EUS-FNA is fully resected during pancreaticoduodenectomy. Some authors discourage performing EUS-FNA in perihilar cholangiocarcinoma, while in the Mayo Clinic liver transplantation protocol, EUS-FNA is considered an absolute contraindication [31].

Another approach to the diagnostic work-up of biliary strictures is the use of IDUS. IDUS provides an accurate image of the bile duct wall and surrounding tissue. Despite the limited depth of penetration, a precise image of an intraductal lesion is often possible, allowing assessment for invasion or compression of adjacent structures. Based on imaging criteria, the accuracy of IDUS in differentiating benign from malignant strictures ranges from 76% to 92% in series of patients with various types of biliary strictures [32-34]. In 2002, Tamada and colleagues [35] proposed other IDUS criteria, including interruption of the bile duct wall, that is considered specific for malignant stricture. Sessile tumors, even when they remain intraductal or extend outside the CBD wall, and tumor size greater than 10 mm are the other major criteria indicating malignancy. Echogenicity of the stricture, which is probably highly operator dependent, is no longer considered a factor predictive of malignancy. The presence of two of the criteria, even with negative biopsies, is highly suspicious of malignancy. The absence of IDUS criteria of malignancy in addition to negative biopsies indicate a benign lesion with a 95% accuracy and 100% NPV.

Due to the low accuracy of each diagnostic modality per se, new options and devices are being developed. Among new diagnostic modalities, peroral cholangioscopy (POC) is the newest representative method that can be used for tissue sampling and imaging in patients with suspected CC. POC allows direct visualization of the bile duct and strictures and guides biopsy targeting. Three studies however, reported a higher accuracy with visual diagnosis compared to histological diagnosis [36-38]. Despite the initial

enthusiasm with this technique there are some drawbacks: the acquisition of adequate tissue samples from biliary strictures in the distal CBD remains difficult, due to difficulty in maintenance of a stable position; the complication rate of ERCP with cholangioscopy has been reported to be higher than with ERCP alone (7% vs. 2.9%), namely cholangitis and pancreatitis [39].

A study by Lee YN *et al.* [40] evaluating the usefulness of a diagnostic approach using peroral cholangioscopy–guided forceps biopsy (POC-FB) or EUS-FNB according to the stricture location in patients with suspected malignant biliary strictures, showed a sensitivity of 96.0% (95% CI 79.7%–99.9%) of EUS-FNB for distal biliary strictures. The initial transpapillary biopsy by ERCP combined with follow-up biopsy using POC-FB in patients with proximal biliary strictures and EUS-FNB in patients with distal biliary strictures showed high overall diagnostic accuracies of 98.3% (95% CI 95.9%–100%) and 98.4% (95% CI 95.3%–100%), respectively.

In a prospective comparative study of 40 patients undergoing ERCP, MRCP, CT, and EUS for biliary strictures, the diagnostic specificity improved when MRCP was combined with EUS [41]. Another prospective study of 142 patients with cholestasis and common hepatic duct dilatation showed that MRCP followed by EUS was highly sensitive and specific (90% and 98%, respectively) for the early diagnosis of extrahepatic bile duct carcinoma [42]. More recently, Nguyen and al reported on the utilization of EUS FNA before considering cholangioscopy in brushing-negative biliary strictures. The need for cholangioscopy was avoided in 60% of patients where EUS FNA provided tissue diagnosis, resulting in reduction of complications by 2.5% and in cost savings [43]. However, in patients with proximal biliary strictures, the performance of EUS FNA remains suboptimal. Siddiqui and colleagues demonstrated that cholangioscopy provided a definitive diagnosis in 77% of patients where ERCP-guided cytology brushing and EUS FNA were both inconclusive [44].

Taking into consideration all the above evidence, the following diagnostic work-up can be proposed:

- For hilar strictures, MRI plus ERCP with IDUS and brush cytology/ biopsy under fluoroscopy or cholangioscopy. EUS FNA can be considered when a strong clinical suspicion for malignancy persists after a negative ERCP-based workup.
- For distal CBD strictures: EUS plus FNA first, followed by ERCP with IDUS and brush cytology/cholangioscopy/ biopsy if needed.

Staging

When the diagnosis of CC is made, the primary aim of staging is to determine if the patient is candidate for surgical resection, which offers the only practical chance of cure. EUS is gaining prominence in CC staging as it can visualize the local extent of the primary tumor, the presence of regional lymphadenopathy and omental metastasis. Table 2 and 3 present the TNM staging criteria for proximal and distal CC respectively.

Multiple studies have established that EUS is superior to alternative imaging modalities that included CT, MRI, abdominal ultrasound, and angiography in detecting tumor vascular invasion and determining resectability in patients with CC [45,46]. Fritscher-Ravens *et al.* demonstrated that EUS correctly identified unresectable diseases in 83% of patients who were confirmed to have loco-regional metastases by exploratory surgery [47]. Similarly, Mohamadnejad found that EUS was more accurate than CT scan in determining the unresectability status (53% vs. 33% respectively) as confirmed by exploratory surgery [48].

Determination of lymph node involvement is another important criterion for treatment

planning in CC. EUS-guided fine needle aspiration (FNA) of tumors and enlarged lymph nodes can also be performed.

Historically adopted EUS imaging features including long-axis length, roundness, echogenicity and homogeneity, individually and collectively have proved to have a poor predictive value for malignancy in this context. Therefore, in patients with CC identified lymph nodes should be sampled irrespective of their morphological or echo features. Gleeson *et al.* compared the accuracy of EUS in detecting malignant lymph nodes and compared them to CT, MRI and laparotomy in a cohort of 47 patients with CC being evaluated for liver transplant [49]. In this study, EUS visualized all suspicious lymph nodes, unlike CT and MRI, which failed to identify the presence of nodes in a quarter of cases. In terms of diagnostic accuracy, EUS-FNA detected metastatic disease in the nodes of 8 of 47 individuals, thus sparing 38% of the cohort from a more invasive diagnostic laparotomy. Of the patients who ultimately did undergo surgical staging, EUS-FNA missed metastatic nodal involvement in 2 patients, with an overall sensitivity of 80%. The identification of invasive or metastatic disease spares patients with unresectable tumors of more invasive staging procedures and by confirming benign disease, EUS avoids unnecessary surgical resections. However, the data currently available is limited and inconsistent, with some studies demonstrating an excellent accuracy for EUS, while others showing only marginal results.

One of the major problems of CC diagnosis and staging is in the evaluation of proximal bile duct lesions, in which the accuracy of imaging modalities is inferior and clinical experience is limited. IDUS is considered to offer advantage over other imaging modalities, with better discrimination of the proximal biliary system and surrounding structures, such as the right hepatic artery, portal vein, and the hepatoduodenal ligament. It detects early lesions, determines the longitudinal tumor extent, and identifies tumor extension into adjacent organs and major blood vessels. However, the depth of penetration is limited to 2 cm, which limits its usefulness in evaluating lymph nodes and metastatic disease. In a prospective study comparing EUS and IDUS in biliary strictures, the accuracy of IDUS in T staging (78%) was higher than that of EUS (54%) [50-53]. Both techniques present limitations in their ability to differentiate T1 from T2 bile duct cancers. To address this deficiency, Tamada *et al.* [54] initially evaluated IDUS in staging of cholangiocarcinoma and concluded that it has an accuracy ranging from 72% to 86% for the assessment of longitudinal cancer extension considering the morphologic criteria used. The assessment of longitudinal spread considering morphological criteria was also evaluated by Inui *et al.* [55] that confirmed the high value of IDUS, with an overall accuracy of 85%. IDUS was also very accurate (100%) in defining portal vein and right hepatic artery involvement, which are the two most frequently involved vessels. In two studies, the accuracy of IDUS in detecting vascular involvement was significantly higher than angiography for both the portal vein (100% vs. 50%) and the right hepatic artery (100% vs. 33%) [50].

Despite the apparently better accuracy of EUS and IDUS in CC staging, controlled series comparing the performance of each imaging modality (CT, MRCP, EUS, and IDUS) are lacking.

Therapeutic role of EUS

These malignancies are often unresectable at the time of presentation, thus making palliation with biliary drainage a widely accepted management option [56-59]. In this context, nonsurgical drainage has shown to be safe, effective, and is currently the standard of care [60-62]. Biliary drainage is most commonly achieved placing a biliary stent by ERCP. In 5% to 10% of cases, biliary drainage by ERCP is not possible due to difficult anatomy/ inability to cannulate the papilla [63]. Percutaneous transhepatic biliary drainage (PTBD) is a well-established alternative in these patients, however associated with increased morbidity, longer length of hospital stay, and higher patient discomfort [64]. A less invasive alternative after an unsuccessful biliary cannulation is endoscopic ultrasound guided biliary drainage (EUS-BD). EUS provides better visualization of the biliary obstruction and facilitates direct access to the biliary tree. This was first described in 2001 by Giovannini *et al.* [65]. Since then, multiple studies have been published describing the techniques, indications, safety, and efficacy of EUS-BD.

EUS-BD can be achieved using 3 different techniques:

- Transluminal, using a transgastric (choledochogastrostomy) or transduodenal (choledochoduodenostomy) approach, in which a stent is placed from the gastrointestinal lumen into the bile duct without accessing the papilla.
- Rendezvous, in which a guide wire is inserted into an extrahepatic or intrahepatic bile duct and then advanced through the papilla. The wire is retrieved in the duodenum and stent is placed transpapillary.
- Antegrade transpapillary biliary stenting, in which after transluminal puncture, a guide wire is passed via the papilla into the duodenum and a stent is then placed in anterograde fashion across the biliary stricture after appropriate dilatation.

A meta-analysis recently published [66], including 528 patients, evaluated the success of EUS-BD in malignant inoperable biliary strictures and compared it to PTBD. In the pooled patient population, EUS-BD was successful in 90% of cases with an overall procedure related complication rate of 16%. The OR for successful biliary drainage in EUS-BD vs. PTBD was 3.06 (95% CI = 1.11–8.43), with a risk difference for overall procedure related complications of -0.21 (95% CI = -0.35 to -0.06) favoring EUS-BD.

This palliative treatment with an acceptably low rate of complications allows a majority of patients to receive chemotherapy after drainage. The main limitation of this type of drainage is the inability to drain the right lobe. In 2012, the European Society of Gastrointestinal Endoscopy stated that more than 50% of the liver had to be drained to increase patient survival in cases of hilar stenosis. Therefore, draining only the left liver is not sufficient to obtain this percentage [67]. Draining the right liver using EUS is challenging because of limited accessibility to this lobe through the stomach or the duodenum, and only few studies have specifically addressed this procedure [68-72]. An approach gaining interest is the bridge technique, in which a stent is inserted between the right and left liver lobe, through the hilum stricture, after creating a hepaticogastrostomy or a hepaticojejunostomy. In 2019, Giovannini *et al.* [73] published a case series of 12 patients submitted to the bridge technique as first line therapy. Technical success was achieved in all patients with a clinical success of 83%. Chemotherapy could be administered in 70% of patients after this procedure. Although presenting as a feasible alternative to drain patients with hilar tumors with inaccessible papilla, the bridge technique requires a high level of technical skills, and should be restricted to specialized centers with high volume of EUS therapeutic procedures.

Table 1. TNM criteria for ampullary cancer by the American Joint Committee on Cancer (8th edition) [74]

Category		Criteria
T category	**Tx**	Primary tumor cannot be assessed
	T0	No evidence of primary tumor
	Tis	Carcinoma *in situ*
	T1	Tumor limited to ampulla of Vater or sphincter of Oddi or tumor invades beyond the sphincter of Oddi (perisphincter invasion) and/or into the duodenal submucosa.
	T1a	Tumor limited to ampulla of Vater or sphincter of Oddi
	T1b	Tumor invades beyond the sphincter of Oddi (perisphincter invasion) and/or into the duodenal submucosa.
	T2	Tumor invades into the muscularis propria of the duodenum
	T3	Tumor directly invades the pancreas (up to 0.5 cm) or tumor extends more than 0.5 cm into the pancreas, or extends into peripancreatic or periduodenal tissue or duodenal serosa without involvement of the celiac axis or superior mesenteric artery
	T3a	Tumor directly invades the pancreas (up to 0.5 cm)
	T3b	Tumor extends more than 0.5 cm into the pancreas, or extends into peripancreatic or periduodenal tissue or duodenal serosa without involvement of the celiac axis or superior mesenteric artery
	T4	Tumor involves the celiac axis, superior mesenteric artery and/or common hepatic artery, irrespective of size
N category	**Nx**	Regional lymph node cannot be assessed
	N0	No regional lymph node metastasis
	N1	Metastasis in 1 – 3 regional lymph nodes
	N2	Metastasis in ≥4 regional lymph nodes
M category	**cM0**	No distant metastasis
	cM1	Distant metastasis
	pM1	Distant metastasis, microscopically confirmed

Table 2. TNM criteria for proximal bile duct cancer by the American Joint Committee on Cancer (8th edition) [74]

Category		Criteria
Primary tumor (T)	**TX**	Primary tumor cannot be assessed
	T0	No evidence of primary tumor
	Tis	Carcinoma in situ/ high grade dysplasia
	T1	Tumor confined to the bile duct, with extension up to the muscle layer or fibrous tissue
	T2	Tumor invades beyond the wall of the bile duct to surrounding adipose tissue, or tumor invades adjacent hepatic parechyma
	T2a	Tumor invades beyond the wall of the bile duct to surrounding adipose tissue
	T2b	Tumor invades adjacent hepatic parechyma
	T3	Tumor invades unilateral branches of the portal vein or hepatic artery
	T4	Tumor invades the main portal veins or its branches bilaterally, or the common hepatic artery; or unilateral second-order biliary radicals with contralateral portal vein or hepatic artery involvement
	T suffix (m)	Select if syncrhonous primary tumors are found in single organ

▸▸

▸▸

Regional lymph nodes (N)	**Nx**	Regional lymph node cannot be assessed
	N0	No regional lymph node metastasis
	N1	One to three positive lymph node typically involving the hilar, cystic duct, common bile duct, hepatic artery, posterior pancreatoduodenal, and portal vein lymph nodes
	N2	Four or more positive lymph nodes from the sites described for N1
	N suffix (sn)	Select regional lymph node metastasis identified by sentinel lymph node biopsy only
	N suffix (f)	Select regional lymph node metastasis identified by FNA or core needle biopsy only
Distant metastasis (M)	**cM0**	No distant metastasis
	cM1	Distant metastasis
	pM1	Distant metastasis, microscopically confirmed

Table 3. TNM criteria for distal bile duct cancer by the American Joint Committee on Cancer (8th edition) [74]

Category		Criteria
T category	**Tx**	Primary tumor cannot be assessed
	Tis	Carcinoma *in situ*/ high grade dysplasia
	T1	Tumor invades the bile duct wall with a depth less than 5 mm
	T2	Tumor invades the bile duct wall with a depth of 5-12 mm
	T3	Tumor invades the bile duct wall with a depth greater than 12 mm
	T4	Tumor involves the celiac axis, superior mesenteric artery and/or common hepatic artery
	T suffix (m)	Select if syncrhonous primary tumors are found in single organ
N category	**Nx**	Regional lymph node cannot be assessed
	N0	No regional lymph node metastasis
	N1	Metastasis in 1-3 regional lymph nodes
	N2	Metastasis in ≥4 regional lymph nodes
	N suffix (sn)	Select regional lymph node metastasis identified by sentinel lymph node biopsy only
	N suffix (f)	Select regional lymph node metastasis identified by FNA or core needle biopsy only
M category	**cM0**	No distant metastasis
	cM1	Distant metastasis
	pM1	Distant metastasis, microscopically confirmed

References

1. Kimchi NA, Mindrul V, Broide E, Scapa E. The contribution of endoscopy and biopsy to the diagnosis of periampullary tumors. Endoscopy. 1998 Aug;30(6):538-43.
2. Ponchon T, Berger F, Chavaillon A, Bory R, Lambert R. *et al.* Contribution of endoscopy to diagnosis and treatment of tumors of the ampulla of Vater. Cancer. 1989 Jul 1;64(1):161-7.
3. Clary BM, Tyler DS, Dematos P, Gottfried M, Pappas TN. Local ampullary resection with careful intraoperative frozen section evaluation for presumed benign ampullary neoplasms. Surgery. 2000 Jun;127(6):628-33.
4. Neoptolemos JP, Talbot IC, Carr-Locke DL, Shaw DE, Cockleburgh R, Hall AW, *et al.* Treatment and outcome in 52 consecutive cases of ampullary carcinoma. Br J Surg. 1987 Oct;74(10):957-61.
5. Yamaguchi K, Enjoji M, Kitamura K. Endoscopic biopsy has limited accuracy in diagnosis of ampullary tumors. Gastrointest Endosc. 1990 Nov-Dec;36(6):588-92.
6. Patel R, Davitte J, Varadarajulu S, Wilcox CM. Endoscopic resection of ampullary adenomas: complications and outcomes. Dig Dis Sci. 2011 Nov;56(11):3235-40.
7. Roberts KJ, McCulloch N, Sutcliffe R, Isaac J, Muiesan P, Bramhall S, *et al*. Endoscopic ultrasound assessment of lesions of the ampulla of Vater is of particular value in low-grade dysplasia. HPB (Oxford). 2013 Jan;15(1):18-23.
8. Catalano MF, Linder JD, Chak A, Sivak MV Jr, Raijman I, Geenen JE, *et al.* Endoscopic management of adenoma of the major duodenal papilla. Gastrointest Endosc. 2004 Feb;59(2):225-32.
9. Ceppa EP, Burbridge RA, Rialon KL, Omotosho PA, Emick D, Jowell PS, *et al.* Endoscopic versus surgical ampullectomy: an algorithm to treat disease of the ampulla of Vater. Ann Surg. 2013 Feb;257(2):315-22.
10. Chen CH, Yang CC, Yeh YH, Chou DA, Nien CK. Reappraisal of endosonography of ampullary tumors: correlation with transabdominal sonography, CT, and MRI. J Clin Ultrasound. 2009 Jan;37(1):18-25.
11. Rivadeneira DE, Pochapin M, Grobmyer SR, Lieberman MD, Christos PJ, Jacobson I, *et al.* Comparison of linear array endoscopic ultrasound and helical computed tomography for the staging of periampullary malignancies. Ann Surg Oncol. 2003 Oct;10(8):890-7.
12. 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 Jul-Aug;29(6):313-21.
13. Okano N, Igarashi Y, Hara S, Takuma K, Kamata I, Kishimoto Y, *et al.* Endosonographic preoperative evaluation for tumors of the ampulla of Vater using endoscopic ultrasonography and intraductal ultrasonography. Clin Endosc. 2014 Mar;47(2):174-7.
14. Ridtitid W, Schmidt SE, Al-Haddad MA, LeBlanc J, DeWitt JM, McHenry L, *et al*. Performance character- istics of EUS for locoregional evaluation of ampullary lesions. Gastrointest Endosc. 2015 Feb;81(2):380-8.
15. 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 Mar;49(3 Pt 1):349-57.
16. Boix J, Lorenzo-Zuniga V, Moreno de Vega V, Domènech E, Gassull MA. Endoscopic resection of ampullary tumors: 12-year review of 21 cases. Surg Endosc. 2009 Jan;23(1):45-9.
17. Itoh A, Goto H, Naitoh Y, Hirooka Y, Furukawa T, Hayakawa T. Intraductal ultrasonography in diagnosing tumor extension of cancer of the papilla of Vater. Gastrointest Endosc. 1997 Mar;45(3):251-60.
18. Baillie J. Endoscopic ampullectomy. Am J Gastroenterol 2005 Nov;100(11):2379-81.
19. Saini S. Imaging of the hepatobiliary tract. N Engl J Med. 1997 Jun 26;336(26):1889-94.
20. Lee HY, Kim SH, Lee JM, Kim SW, Jang JY, Han JK, *et al.* Preoperative assessment of resectability of hepatic hilar cholangiocarcinoma: combined CT and cholangiography with revised criteria. Radiology. 2006 Apr;239(1):113-21.
21. Aloia TA, Charnsangavej C, Faria S, Ribero D, Abdalla EK, Vauthey JN, *et al.* High-resolution computed tomography accurately predicts resectability in hilar cholangiocarcinoma. Am J Surg. 2007 Jun;193(6):702-6.
22. Rizvi S, Gores GJ. Pathogenesis, diagnosis, and management of cholangiocarcinoma. Gastroenterology 2013 Dec;145(6):1215-29.
23. Blechacz B, Komuta M, Roskams T, Gores GJ. Clinical diagnosis and staging of cholangiocarcinoma. Nat Rev Gastroenterol Hepatol. 2011 Aug 2;8(9):512-22.
24. Navaneethan U, Njei B, Lourdusamy V, Konjeti R, Vargo JJ, Parsi M. Comparative effectiveness of biliary brush cytology and intraductal biopsy for detection of malignant biliary strictures: a systematic review and meta-analysis. Gastrointest Endosc. 2015 Jan;81(1):168-76.
25. Moreno Luna LE, Kipp B, Halling KC, Sebo TJ, Kremers WK, Roberts LR, *et al.* Advanced cytologic techniques for the detection of malignant pancreatobiliary strictures. Gastroenterology. 2006 Oct;131(4):1064-72.
26. Nanda A, Brown JM, Berger SH, Lewis MM, Barr Fritcher EG, *et al.* Triple modality testing by endoscopic retrograde cholangiopancreatography for the diagnosis of cholangiocarcinoma. Therap Adv Gastroenterol. 2015 Mar;8(2):56-65.

27. Sadeghi A, Mohamadnejad M, Islami F, Keshtkar A, Biglari M, Malekzadeh R, *et al.* Diagnostic yield of EUS-guided FNA for malignant biliary stricture: a systematic review and meta-analysis. Gastrointest Endosc 2016 Feb;83(2):290-8.e1.
28. Rösch T, Hofrichter K, Frimberger E, Meining A, Born P, Weigert N, *et al.* ERCP or EUS for tissue diagnosis of biliary strictures? A prospective comparative study. Gastrointest Endosc 2004 Sep;60(3):390-6.
29. Lee JH, Salem R, Aslanian H, Chacho M, Topazian M. Endoscopic ultrasound and fine-needle aspiration of unexplained bile duct strictures. Am J Gastroenterol 2004 Jun;99(6):1069-73.
30. Paquin SC, Gariepy G, Lepanto L, Bourdages R, Raymond G, Sahai AV. A first report of tumor seeding because of EUS-guided FNA of a pancreatic adenocarcinoma. Gastrointest Endosc. 2005 Apr;61(4):610-1.
31. Rosen CB, Heimbach JK, Gores GJ. Liver transplantation for cholangiocarcinoma. Transpl Int. 2010 Jul;23(7):692-7.
32. Varadarajulu S, Eloubeidi MA, Wilcox CM. Prospective evaluation of indeterminate ERCP findings by intraductal ultrasound. J Gastroenterol Hepatol. 2007 Dec;22(12):2086-92.
33. Vazquez-Sequeiros E, Baron TH, Clain JE, Gostout CJ, Norton ID, Petersen BT, *et al*. Evaluation of indeterminate bile duct strictures by intraductal US. Gastrointest Endosc. 2002 Sep;56(3):372-9
34. Tamada K, Nagai H, Yasuda Y, Tomiyama T, Ohashi A, Wada S, *et al.* Transpapillary intraductal US prior to biliary drainage in the assessment of longitudinal spread of extrahepatic bile duct carcinoma. Gastrointest Endosc. 2001 Mar;53(3):300-7.
35. Tamada K, Tomiyama T, Wada S, Ohashi A, Satoh Y, Ido K, *et al.* Endoscopic transpapillary bile duct biopsy with the combination of intraductal ultrasonography in the diagnosis of biliary strictures. Gut. 2002 Mar;50(3):326-31.
36. Korrapati P, Ciolino J, Wani S, Shah J, Watson R, Muthusamy VR, *et al.* The efficacy of peroral cholangioscopy for difficult bile duct stones and indeterminate strictures: a systematic review and meta-analysis. Endosc Int Open. 2016 Mar;4(3):E263-75.
37. Nishikawa T, Tsuyuguchi T, Sakai Y, Sugiyama H, Miyazaki M, Yokosuka O. Comparison of the diagnostic accuracy of peroral video-cholangioscopic visual findings and cholangioscopy-guided forceps biopsy findings for indeterminate biliary lesions: a prospective study.Gastrointest Endosc. 2013 Feb;77(2):219-26
38. Ramchandani M, Reddy DN, Gupta R, Lakhtakia S, Tandan M, Darisetty S, *et al.* Role of single-operator peroral cholangioscopy in the diagnosis of indeterminate biliary lesions: a single-center, prospective study. Gastrointest Endosc. 2011 Sep;74(3):511-9.
39. Sethi A, Chen YK, Austin GL, Brown WR, Brauer BC, Fukami NN, *et al.* ERCP with cholangiopancreatoscopy may be associated with higher rates of complications than ERCP alone: a single-center experience. Gastrointest Endosc. 2011 Feb;73(2):251-6.
40. Lee YN, Moon JH, Choi HJ, Kim HK, Lee HW, Lee TH, *et al.* Tissue acquisition for diagnosis of biliary strictures using peroral cholangioscopy or endoscopic ultrasound-guided fine-needle aspiration. Endoscopy. 2019. Jan;51(1):107
41. Rösch T, Meining A, Frühmorgen S, Zillinger C, Schusdziarra V, Hellerhoff K, *et al.* A prospective comparison of the diagnostic accuracy of ERCP, MRCP, CT, and EUS in biliary strictures. Gastrointest Endosc. 2002 Jun;55(7):870-6.
42. Sai JK, Suyama M, Kubokawa Y, Watanabe S, Maehara T. Early detection of extrahepatic bile-duct carcinomas in the nonicteric stage by using MRCP followed by EUS. Gastrointest Endosc. 2009 Jul;70(1):29-36.
43. Nguyen NQ, Schoeman MN, Ruszkiewicz A. Clinical utility of EUS before cholangioscopy in the evaluation of difficult biliary strictures. Gastrointest Endosc. 2013 Dec;78(6):868-874.
44. Siddiqui AA, Mehendiratta V, Jackson W, Loren DE, Kowalski TE, Eloubeidi MA. Identification of cholangiocarcinoma by using the Spyglass Spyscope system for peroral cholangioscopy and biopsy collection. Clin Gastroenterol Hepatol. 2012 May;10(5):466-71; quiz e48.
45. Eloubeidi MA, Chen VK, Jhala NC, Eltoum IE, Jhala D, Chhieng DC, *et al*. Endoscopic ultrasound-guided fine needle aspiration biopsy of suspected cholangiocarcinoma. Clin Gastroenterol Hepatol. 2004 Mar;2(3):209-13.
46. Sugiyama M, Hagi H, Atomi Y, Saito M. Diagnosis of portal venous invasion by pancreatobiliary carcinoma: value of endoscopic ultrasonography. Abdom Imaging. 1997 Jul-Aug;22(4):434-8.
47. Fritscher-Ravens A, Broering DC, Knoefel WT, Rogiers X, Swain P, Thonke F, *et al.* EUS-guided fine-needle aspiration of suspected hilar cholangiocarcinoma in potentially operable patients with negative brush cytology. Am J Gastroenterol. 2004 Jan;99(1):45-51.
48. Mohamadnejad M, DeWitt JM, Sherman S, LeBlanc JK, Pitt HA, House MG, *et al.* Role of EUS for preoperative evaluation of cholangiocarcinoma: a large single-center experience. Gastrointest Endosc. 2011 Jan;73(1):71-8.
49. Gleeson FC, Rajan E, Levy MJ, Clain JE, Topazian MD, Harewood GC, *et al.* EUS-guided FNA of regional lymph nodes in patients with unresectable hilar cholangiocarcinoma. Gastrointest Endosc. 2008 Mar;67(3):438-43
50. Tamada K, Ido K, Ueno N, Ichiyama M, Tomiyama T, Nishizono T, *et al.* Assessment of portal vein invasion by bile duct cancer using intraductal ultrasonography. Endoscopy. 1995 Oct;27(8):573-8.
51. Kuroiwa M, Tsukamoto Y, Naitoh Y, Hirooka Y, Furukawa T, Katou T. New technique using intraductal ultrasonography for the diagnosis of bile duct cancer. J Ultrasound Med. 1994 Mar;13(3):189-95.
52. Tamada K, Ido K, Ueno N, Kimura K, Ichiyama M, Tomiyama T. Preoperative staging of extrahepatic bile duct cancer with intraductal ultrasonography. Am J Gastroenterol 1995 Feb;90(2):239-46.

53. Menzel J, Poremba C, Dietl KH, Domschke W. Preoperative diagnosis of bile duct strictures–comparison of intraductal ultrasonography with conventional endosonography. Scand J Gastroenterol. 2000 Jan;35(1):77-82.
54. Tamada K, Ueno N, Ichiyama M, Tomiyama T, Nishizono T, Wada S, *et al.* Assessment of pancreatic parenchymal invasion by bile duct cancer using intraductal ultrasonography. Endoscopy. 1996 Aug;28(6):492-6.
55. Inui K, Miyoshi H. Cholangiocarcinoma and intraductal sonography. Gastrointest Endosc Clin N Am. 2005 Jan;15(1):143-55, x.
56. Shepherd HA, Royle G, Ross AP, Diba A, Arthur M, Colin-Jones D. Endoscopic biliary endoprosthesis in the palliation of malignant obstruction of the distal common bile duct: a randomized trial. Br J Surg. 1988 Dec;75(12):1166-8.
57. Smith AC, Dowsett JF, Russell RC, Hatfield AR, Cotton PB. Randomised trial of endoscopic stenting versus surgical bypass in malignant low bileduct obstruction. Lancet. 1994 Dec 17;344(8938):1655-60.
58. Speer AG, Cotton PB, Russell RC, Mason RR, Hatfield AR, Leung JW, *et al.* Randomised trial of endoscopic versus percutaneous stent insertion in malignant obstructive jaundice. Lancet. 1987 Jul 11;2(8550):57-62.
59. Andersen JR, Sørensen SM, Kruse A, Rokkjaer M, Matzen P. Randomised trial of endoscopic endoprosthesis versus operative bypass in malignant obstructive jaundice. Gut. 1989 Aug;30(8):1132-5.
60. Gupta K, Mallery S, Hunter D, Freeman ML. Endoscopic ultrasound and percutaneous access for endoscopic biliary and pancreatic drainage after initially failed ERCP. Rev Gastroenterol Disord. 2007 Winter;7(1):22-37.
61. ASGE Guidelines for Clinical Application. The role of ERCP in diseases of the biliary tract and pancreas. American Society for Gastrointestinal Endoscopy. Gastrointest Endosc. 1999 Dec;50(6):915-20.
62. Rösch T, Triptrap A, Frimberger E, Allescher HD, Ott R, *et al.* Long-term results of percutaneous transhepatic biliary drainage for benign and malignant bile duct strictures. Scand J Gastroenterol. 1998 May;33(5):544-9.
63. Enochsson L, Swahn F, Arnelo U, Nilsson M, Löhr M, Persson G. Nationwide, population-based data from 11,074 ERCP procedures from the Swedish Registry for Gallstone Surgery and ERCP. Gastrointest Endosc. 2010 Dec;72(6):1175-84, 1184.e1-3.
64. Voegeli DR, Crummy AB, Weese JL. Percutaneous transhepatic cholangiography, drainage, and biopsy in patients with malignant biliary obstruction. An alternative to surgery. Am J Surg. 1985 Aug;150(2):243-7.
65. Giovannini M, Moutardier V, Pesenti C, Bories E, Lelong B, Delpero JR. Endoscopic ultrasound-guided bilioduodenal anastomosis: a new technique for biliary drainage. Endoscopy 2001 Oct;33(10):898-900.
66. Moole H, Bechtold ML, Forcione D, Puli SR. A meta-analysis and systematic review: Success of endoscopic ultrasound guided biliary stenting in patients with inoperable malignant biliary strictures and a failed ERCP. Medicine (Baltimore). 2017 Jan;96(3):e5154.
67. Dumonceau JM, Tringali A, Blero D, Devière J, Laugiers R, Heresbach D*, et al.* Biliary stenting: Indications, choice of stents and results: European Society of Gastrointestinal Endoscopy (ESGE) Clinical Guideline. Endoscopy. 2012 Mar;44(3):277-98.
68. Ogura T, Sano T, Onda S, Imoto A, Masuda D, Yamamoto K, *et al.* Endoscopic ultrasound-guided biliary drainage for right hepatic bile duct obstruction: Novel technical tips. Endoscopy. 2015 Jan;47(1):72-5.
69. Moryoussef F, Sportes A, Leblanc S, Bachet JB, Chaussade S, Prat F. Is EUS-guided drainage a suitable alternative technique in case of proximal biliary obstruction? Therap Adv Gastroenterol. 2017 Jul;10(7):537-544.
70. Ogura T, Onda S, Takagi W, Sano T, Okuda A, Masuda D, *et al.* Clinical utility of endoscopic ultrasound-guided biliary drainage as a rescue of re-intervention procedure for high-grade hilar stricture. J Gastroenterol Hepatol. 2017 Jan;32(1):163-168.
71. Park SJ, Choi JH, Park DH, Choi JH, Lee SS, Seo DW, *et al.* Expanding indication: EUS-guided hepaticoduodenostomy for isolated right intrahepatic duct obstruction (with video). Gastrointest Endosc. 2013 Aug;78(2):374-80.
72. Mukai S, Itoi T, Tsuchiya T, Tanaka R, Tonozuka R. EUS-guided right hepatic bile duct drainage in complicated hilar stricture. Gastrointest Endosc. 2017 Jan;85(1):256-257.
73. Caillol F, Bosshardt C, Reimao S, Francioni E, Pesenti C, Bories E, *et al.* Drainage of the right liver under EUS guidance: A bridge technique allowing drainage of the right liver through the left liver into the stomach or jejunum. Endosc Ultrasound. 2019 Mar 12.
74. American Joint Committee on Cancer. Digestive System. Amin MB, Edge S, Greene F, Byrd DR, Brookland RK, et al, eds. AJCC Cancer Staging Manual. 8th edition. New York, NY: Springer. 2016.

6

Rectal and Anal Cancer

Sílvia Leite

KEY POINTS

- EUS is effective for staging the depth of invasion of rectal cancer. It is better for superficial rectal cancer (T1/T2), especially for early rectal tumors, and offers less value in locally advanced rectal cancer (T3/T4).
- EUS is not particularly accurate for staging lymph node involvement in rectal cancer, similar to MRI.
- EUS is not indicated for restaging of rectal cancer after neoadjuvant therapy, with low accuracy for T-stage and N-stage in this context. Restaging MRI appears to have a role to reassess circunferencial resection margin.
- For rectal cancer surveillance after treatment without total mesorectal excision, EUS may be performed in association with sigmoidoscopy.
- Endoanal ultrasound (EAUS) seems effective for anal cancer staging to determine tumor size and depth of invasion into the sphincter complex, with a suggested advantage over MRI in the evaluation of small tumors on the surface of the anal canal (small T1 lesions).
- EAUS cannot visualize anal cancer regional lymph nodes, other than perirectal, so MRI is needed for N-staging.
- EAUS is not recommended for routine surveillance of anal cancer after treatment.
- Experience of the operator, annual volume of cases performed at the center, and the MRI available technology, should be taken in account when deciding the best locoregional staging modalitiy.

Endoscopic ultrasound for rectal cancer

Introduction

The incidence of rectal cancer in the European Union is 125000 per year, i.e. 35% of the total colorectal cancer (CRC) incidence. The mortality is 4–10/100000 population per year [1]. In the United States 43030 new cases of rectal cancer was estimated in 2018 (25920 cases in men, 17110 in women) being CRC the 4th most frequent cancer and 2th leading cause of cancer death [2]. Despite of the improvement in the overall CRC incidence rate as a result of cancer prevention and screening, it has been increasing in patients younger than 50 years, as found on the Surveillance, Epidemiology, and End Results (SEER) CRC registry [3].

Once the diagnosis of rectal cancer is established, the local and distant extent of disease is determined to provide a framework for discussing therapy and defining prognosis. While early lesions (cT1N0M0) with minimal invasion may be effectively treated with local excision with endoscopic submucosal dissection or transanal local excision, ideally transanal endoscopic microsurgery (TEM), cT2-4 disease requires more extensive surgery with total mesorectal excision (TME). In this category, a subset of patients requires preoperative neoadjuvant therapy with chemoradiation (CRT) (cT3-4 or node-positive disease) [4].

The staging system for CRC is the tumor, node, metastasis (TNM) staging system of the combined American Joint Committee on Cancer (AJCC) / Union for International Cancer Control (UICC). The 8th edition revision of the TNM staging classification [5] shown in table 1, contains few changes compared with the earlier 2010 7th edition. It is important to remember that in lower rectum, because of typical absence of peritoneal covering, T4a is not applicable.

The location of the tumor within the rectum is also important to define the type of surgery. Rectum is variable in its absolute length, but is often referred to as that part of large gut extending up to 15 cm from anal verge. Cancers are categorized as low (up to 5 cm), middle (from >5 to 10 cm) or high (from >10 up to 15 cm) by ESMO guidelines [1]. In low rectal tumors preoperative CRT may enhance the ability to preserve the anal sphincter.

Another important prognostic factor is the circunferencial resection margin (CRM) in millimeters. A "positive" CRM, defined variably as a tumor that invades or is in close proximity to the mesorectal fascia (MRF), is the most important risk factor for local recurrence after rectal cancer surgery. If the MRF is involved or if the tumor extends to a point that is within 1 to 2 mm of the MRF, there is a clear risk that the CRM will be involved if only a local excision is performed. As a result, these patients are usually approached with initial CRT [6]

Multiple modalities have been used for staging rectal cancer, including endoscopic ultrasound (EUS), computed tomography (CT), magnetic resonance imaging (MRI) and positron emission tomography.

Table 1. American Joint Committee on Cancer and International Union Against Cancer TNM classification for colon and rectal cancer, 8th edition [5].

Category		Criteria
Primary tumor (T)	**TX**	Primary tumor cannot be assessed
	T0	No evidence of primary tumor
	Tis	Carcinoma in situ / intramucosal adenocarcinoma (involvement of lamina propria with no extension through the muscularis mucosa)
	T1	Tumor invades the submucosa
	T2	Tumor invades the muscularis propria
	T3	Tumor invades through the muscularis propria into pericolorectal tissues
	T4	Tumor invades the visceral peritoneum or invades or adheres to adjacent organ or structure
	T4a	Tumor invades through the visceral peritoneum
	T4b	Tumor invades or adheres to adjacent organ or structure
Regional lymph nodes (N)	**Nx**	Regional lymph nodes cannot be assessed
	N0	No regional lymph node metastasis
	N1	Metastasis in 1–3 regional lymph nodes
	N1a	Metastasis in 1 regional lymph nodes
	N1b	Metastasis in 2–3 regional lymph nodes
	N1c	Tumor deposit(s), i.e. satellites, in the subserosa, or in nonperitonealised pericolic or perirectal soft tissue without regional lymph node metastasis
	N2	Metastasis in 4 or more regional lymph nodes
	N2a	Metastasis in 4–6 regional lymph nodes
	N2b	Metastasis in 7 or more regional lymph nodes
Distant metastasis (M)	**cM0**	No distant metastasis
	cM1	Distant metastasis
	cM1a	Metastasis confined to one organ [liver, lung, ovary, non-regional lymph node(s)] without peritoneal metastases
	cM1b	Metastasis in more than one organ
	cM1c	Metastasis to the peritoneum with or without other organ involvement

Rectal endoscopic ultrasound (EUS)

Rectal EUS is performed by using a radial or, more recently and frequently, a curvilinear echoendoscope, with high frequency, usually 10 Hz. It can also be performed with radial rigid instruments, with the advantage of being substantially less expensive, but with major limitations such as their restricted ability to image and perform fine needle aspiration (FNA) in the proximal rectum, and evaluate for lymphadenopathy in the region of the left iliac vessels.

It is important to accurately locate the tumor, in relation to the seminal vesicles in males and the cervix in females, in order to clarify the lesion location in relation to the anterior peritoneal reflection.

Rectal cancer usually appears as a hypoechoic lesion that disrupts the normal five-layer sonographic structure of the rectal wall. T1 lesions do not extend beyond the submucosa, defined as the third echo layer on EUS – Fig. 1a. T2 lesions are seen to extend up to but not penetrate through the fourth hypoechoic layer (corresponds to the muscularis propria) – Fig. 1b. T3 lesions penetrate the five echo layers into the perirectal space – Fig. 1c. A T4 lesion invades the visceral peritoneum or involves the adjacent organs such as the prostate, bladder, seminal vesicles, or vagina. The prefix “u” is used to describe ultrasound staging of rectal cancer.

The N-staging of rectal cancer is determined by assessing the perirectal lymph nodes for changes indicating malignant infiltration. These nodes are

usually round and hypoechoic and have a regular border – Fig. 1d. Although described different size cutoffs (ex. ≥5 or ≥10 mm) for malignant lymph nodes, any node seen in a patient with rectal cancer should be closely assessed for malignancy as EUS does not normally visualize lymph nodes in the perirectal region. This is controversial, as a prospective study by Gleeson *et al.* using EUS-FNA showed that only two nodal features could adequately predict malignancy – short-axis length ≥5 mm (odds ratio =2.7) and hypoechogenic appearance (odds ratio =3.8). Also concluded that a threshold number of positive echo criteria would not be feasible to predict nodal disease as only the presence of all four criteria could reliably identify an involved node, which was seen only in 23% of cases [7]. Another challenge in the identification of nodes with EUS is the inability to visualize nodes that are outside the range of the transducer.

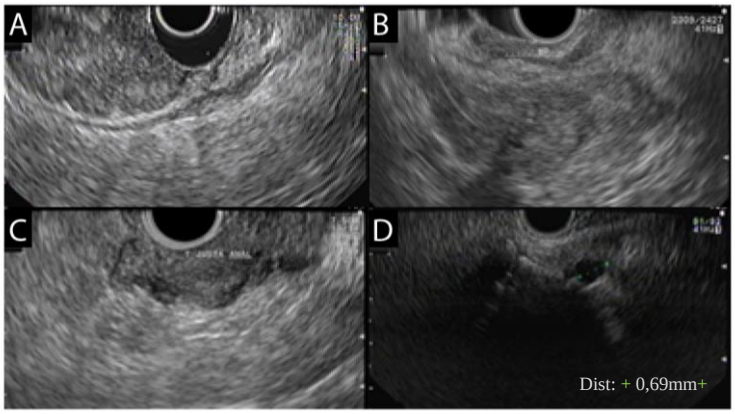

Figure 1. A. uT1 rectal tumor; **B.** uT2 rectal tumor; **C.** uT3 rectal tumor; **D.** perirectal lymph node

EUS for rectal cancer T staging

The largest meta-analysis to date, by Puli *et al*., evaluated accuracy of EUS for T-stage comparing with that determined by surgical histopathology (42 studies, 5039 patients) and described a sensitivity (S) of >80% and a specificity (Sp) of >90%. The authors calculated the pooled S and Sp of EUS to be 87.8% and 98.3% for T1 lesions; 80.5 and 95.6%, for T2 lesions; 96.4% and 90.6%, for T3 lesions; and 95.4% and 98.3%, for T4 cancer. The authors concluded that EUS is accurate for T-staging of rectal cancer [8].

A retrospective study of 6 year experience of EUS for preoperative staging in 192 patients with rectal cancer obtained an accuracy for overall T staging of 86.5%, and for T1, T2, T3, and T4, the accuracy rates were 86.7%, 94.0%, 86.2%, and 65.5%, respectively. So, the authors also concluded that EUS is safe and effective for preoperative staging of rectal cancer and should be a routine examination before surgery, being is particularly effective for T-stage [9].

A very recent prospective study, by Gao *et al.*, in 2019, evaluated the accuracy of EUS for preoperative staging of rectal cancer and guiding the treatment of TEM in early rectal cancer. 126 patients were staged and the results were compared with postoperative histopathology. The overall accuracies of EUS for T and N stage were 90.8% and 76.7%, respectively. The accuracy of EUS for uT1, uT2, uT3, and uT4 stages was 96.8%, 92.1%, 84.1%, and 88.9%, respectively, and for uN0, uN1, and uN2 stages, was 71.9%, 64.9%, and 93.0%, respectively. Twelve patients underwent TEM and received confirmed pathology results of early rectal cancer. After postoperative follow-up, there were no local recurrences or distant metastases. The authors concluded that EUS is a good and comparable technique for postoperative staging of rectal cancer. Moreover, EUS is used as

indicator for preoperative staging and tumor assessment strategy when considering TEM [10].

But other studies showed different findings. Marusch *et al*. conducted a large, multicenter, prospective study which looked at data from more than 300 centers in Germany (N=7096) to analyze the accuracy of EUS in staging rectal cancer in routine clinical practice, by calculating the degree of correspondence between uT-stage and T-stage on histopathological examination. The value of this correspondence was calculated by the authors to be 64.7%. Of the 35.3% of cases, when the T-stage was not found to correspond, 18% was due to understaging by EUS and 17.3% was due to EUS overstaging. T2 and T4 lesions were reported to have a lower rate of correlation than T1 and T3 lesions [11].

Also, Ashrat *et al*. reports the accuracy of EUS in preoperative staging and impact for patients entered on the UK TEM database. EUS was performed in 165 of 494 patients who underwent TEM for rectal cancer. It inaccurately staged rectal cancer in 44.8% of tumors: 32.7% were understaged and 12.1% were overstaged. The data showed that EUS is employed in a minority of patients with rectal cancers undergoing TEM in the UK and its accuracy in this 'Real World' practice is still disappointing [12].

As a conclusion and with agreement with international guidelines: EUS may define treatment for the earliest tumors, being of less value in locally advanced rectal cancer [1]. uT1 tumors appropriate for TEM can be selected by determining whether a lesion is limited to the mucosa or submucosa. Also in the newest NCCN guideline 2019 [13] EUS is recommended for rectal cancer staging if MRI is contraindicated and could be considered for superficial lesions.

Magnification chromoendoscopy, EUS and MRI are considered complementary staging modalities for early rectal cancer by the European Association for Endoscopic Surgery [14].

EUS for rectal cancer N staging

Studies report variable results, being EUS for N-stage less accurate than for T-stage, with similar results to MRI.

Puli *et al.* conducted a meta-analysis to determine the accuracy of EUS for N staging of rectal cancer (35 studies, 2732 patients). EUS pooled S and Sp was 73.2% 75.8%, respectively. The positive likelihood ratio was 2.84 and negative likelihood ratio was 0.42. Comparing the modest positive likelihood ratio to the low-negative likelihood ratio, the authors concluded that EUS had more utility in excluding nodal invasion rather than confirming the presence of node-positive disease [15].

The use of EUS-FNA to theoretically increase accuracy has been a matter of debate. EUS-FNA has more utility in early T-stages (T1/ T2) where the presence of involved nodes would upstage the disease and change the management of the patient. Furthermore, it is of note that EUS-FNA cannot be performed in those cases where sampling of nodes would require passage of the needle through the primary tumor (i.e., peritumoral nodes).

EUS versus computed tomography and magnetic resonance imaging

Bipat *et al.* performed a meta-analysis in 2004, including 90 studies, to compare accuracy of EUS, CT and MRI for staging rectal cancer [16]. For muscularis propria invasion (T2), EUS and MRI imaging had similar S; Sp of EUS (86%) was significantly higher than that of MRI imaging (69%). For perirectal tissue invasion, S of EUS (90%) was significantly higher than that of CT (79%) and MRI (82%); Sp were comparable. For lymph node involvement, estimates for EUS, CT, and MRI imaging were comparable (EUS, S 67% and Sp 78%; MRI, S 66% and Sp 76%). They

concluded that for local invasion, EUS was the most accurate modality.

Compared to EUS, MRI is inferior in early lesion staging due to its limited visualization of the rectal submucosa [17], conferring EUS the advantage of assessing T1 tumors that could be managed by TEM (mucosa vs. submucosa involvement) [18].

However, MRI is more precise in visualizing the perirectal fat, MRF and peritoneal involvement, extramural venous invasion as well as surrounding organ infiltration. It can also evaluate the intersphincteric space or levator ani muscle involvement [18].

Also, with the advent of newer developments in MRI technology such as the endorectal coil, phased-array surface coil, and 3.0T MRI, the accuracy of this modality for the T-staging has vastly improved, but still is lower for T1 lesions, and high-quality MRI allows further subclassification of cT3 (by depth of invasion beyond the muscularis propria, in mm).

CT scanning plays an important role in the assessment of systemic spread of rectal cancer but has a limited role in locoregional staging.

EUS disadvantages for rectal cancer staging

The major limitations described for EUS are: impossibility to measure distance to the CRM, operator dependency, inability to detect lymph nodes outside the range of the transducer, overstaging ulcerated lesions and no assessment of stenotic tumors [11-12, 7].

In Marusch *et al.* study [11] the authors sought to compare the hospital EUS volume with the degree of uT-pT correspondence. It was seen that uT-pT correspondence was 63.2% for centers which performed ≤10 EUS per year, 64.6% for those performing 11–30 EUS per year, and 73.1% for those with a EUS case load of >30 per year. Thus, it was hypothesized that EUS in routine clinical practice does not match the accuracy reported in literature and that accuracy of EUS improved with greater experience and volume of cases performed in the center.

In Gleeson *et al.* study [7] for ulcerated and nontraversable stenotic lesions, the results of EUS staging could be doubtful. The accuracy of T staging between nontraversable stenotic lesions and traversable lesions was also significantly different (p=0.002).

EUS restaging after rectal cancer neoadjuvant therapy

Restaging after CRT is a challenge for all imaging modalities due to CRT induced changes, such as fibrosis, edema, inflammation, and necrosis, with risk of overstaging [19].

In a prospective study with 85 locally advanced rectal cancer patients by Marone *et al.* in 2011, EUS for restaging had an overall accuracy of 61% and 59% for T and N-stage, respectively. But, in the control group, those who underwent surgery directly, the accuracy of EUS in staging locally advanced rectal cancer was 86% and 58% for T and N-stage, respectively, which enabled appropriate decision-making [20].

A meta-analysis by Memon *et al.* in 2015 (63 studies) compared MRI and EUS in restaging. Overall, EUS T-stage accuracy (65%) was non-significantly higher than MRI T-stage accuracy (52%). The accuracy of restaging imaging is different for different pathological T stages and highest for T3 tumors. Restaging MRI and EUS were equivalent for prediction of nodal status, but MRI appeared to have a role in excluding CRM involvement. The accuracy of both investigations was 72%, with over-staging and under-staging occurring in 10-15% [21].

As a conclusion, EUS has not been extensively studied in this scenario, but it has been suggested that its routine use for staging purposes following such therapy should be discouraged. MRI is recommended by ESMO and NCCN guidelines, mainly by is role in CRM reassessment.

EUS for rectal cancer surveillance

In cases where TME is not performed (including transanal local excision, TEM and endoscopic submucosal dissection) there is a rationale for periodic examination of the rectum using sigmoidoscopy or EUS. Presently, it is unclear which of these 2 modalities is better, or what the ideal surveillance intervals should be, although EUS has the potential for detection of extraluminal recurrence before development of intraluminal endoscopic findings. Some studies also report that approximately 10% of rectal cancer recurrences are diagnosed by EUS only, and missed by other modalities, including proctoscopy [22]. However, there are no controlled trials evaluating whether intensive EUS improves the survival of patients with rectal cancer.

The American Cancer Society and the US Multi-Society Task Force recommend sigmoidoscopy or EUS every 3 to 6 months for the first 2 years after resection without TME [23].

The NCCN guidelines recommend sigmoidoscopy with EUS or MRI every 3 to 6 months for the first 2 years and then every 6 months until 5 years after transanal local excision [13].

Endoscopic ultrasound for anal cancer

Introduction

Anal cancer involving the anus, anal canal and anorectum is considered a rare type of cancer, accounting for 1%-2% of all digestive tract tumors and 2%–4% of colon, rectal and anal tumors [24]. In the United States in 2018 an annual incidence of 8580 new cases was estimated, with a 1.9 times as many women as men [2] and an estimated 1160 deaths [2]. In Europe, approximately 2000 males and 2300 females are diagnosed with anal cancer every year, and the 5-year survival varies between 66% (Central Europe) and 44% (Eastern Europe) [24]. Importantly, the frequency of anal cancer has increased, especially among men, (approximately 1.9 fold for men and 1.5 for women in the United States from the 1970s through the 2000s).

Although short, the anal canal can host a number of tumor types, reflecting its complex anatomical and histological structure. Histological tumor types are classified according to the World Health Organization (WHO) system [25]. Squamous cell cancers (SCC) account for 75%-80% of cancers of the anal canal. Most series that report outcomes on anal cancer refer exclusively to SCC and most guidelines on management of anal cancer are only addressed to SCC [24, 26-28]. Other less common anal canal tumors include adenocarcinomas, small cell (anaplastic) carcinomas, undifferentiated carcinomas and malignant melanomas.

The anatomic landmarks of the anus could be difficult to identify and exists various definitions of the anal canal (functional/surgical; anatomic; histologic). A simplified taxonomy of the anus has been suggested [29] and it is included in 8th Edition of AJCC Cancer Staging Manual [30], defining anal canal cancer as lesions that cannot be completely visualized with gentle traction placed on the buttocks, whereas a perianal cancer (which replaces the term anal margin) lesion can be completely visualized with gentle traction placed on the buttocks and that is still within 5 cm of the anal orifice. Any lesion >5 cm from the anal orifice would be classified as a skin lesion and would not be considered related to the GI tract.

Primary rectal SCCs, which are very rare, can be difficult to distinguish from anal cancers, and they should be treated according to the same approach as anal cancer.

At the time of diagnosis the majority of patients with anal cancer are potentially curable, and there is an inverse relationship between stage of disease and survival [28, 31]. Large studies have documented that close to 50% of patients with anal cancer present with localized node-negative disease, with high cure rates; 25% of patients present with node-positive disease, whereas only 10% to 15% present with distant metastases.

Treatment aims to cure the patient and to reach the best possible local control, whilst maintaining a functional sphincter. In the past twenty years, sphincter-conserving treatments based on the use of CRT have been developed [32].

Anal cancer staging

Accurate staging is essential to define treatment and prognosis. Anal canal carcinomas are widely classified according to the TNM classification by American Joint Committee on Cancer and International Union Against Cancer [30], as shown in Table 2. This staging system defines T stage by maximum tumor diameter. Nodal status is based on the distance from the primary site rather than the number of nodes involved. Tumor size (T stage) and nodal status (N stage) are considered the most significant prognostic factors for patients with SCC. But this staging system does not take into account muscle sphincter and perianal skin involvement or the presence of a perianal or anovaginal fistula, which are also important prognostic factors that have not been well studied in the era of modern CRT [28].

Table 2. American Joint Committee on Cancer and International Union Against Cancer TNM classification for anal cancer, 8th edition [30].

Category		Criteria
Primary tumor (T)	**TX**	Primary tumor cannot be assessed
	T0	No evidence of primary tumor
	Tis	High-grade squamous intraepithelial lesion (previously termed *carcinoma in situ*, *Bowen disease, anal intraepithelial neoplasia II–III, high-grade anal intraepithelial neoplasia*)
	T1	Tumor ≤2 cm
	T2	Tumor >2 cm but ≤5 cm
	T3	Tumor >5 cm
	T4	Tumor of any size invading adjacent organ(s), such as vagina, urethra, or bladder
Regional lymph nodes (N)	**Nx**	Regional lymph nodes cannot be assessed
	N0	No regional lymph node metastasis
	N1	Metastasis in inguinal, mesorectal, internal iliac, or external iliac nodes
	N1a	Metastasis in inguinal, mesorectal, or internal iliac lymph nodes
	N1b	Metastasis in external iliac lymph nodes
	N1c	Metastasis in external iliac with any N1a nodes
Distant metastasis (M)	**Mx**	Distant metastasis cannot be assessed
	cM0	No distant metastasis
	cM1	Distant metastasis
	pM1	Distant metastasis, microscopically confirmed

Endoanal ultrasound for anal cancer staging

In endoanal ultrasound (EAUS) no special patient preparation is required. A standard radial, rigid probe, 7–10-MHz, is used. The examiner obtains a real-time axial image that is two or three dimensional, depending on the device. Some considerations with EAUS include that it is operator dependent and may cause significant discomfort in patients with anal stenosis.

The EAUS staging more recently used is a modification of a 1984 TNM staging system, proposed by Tarantino *et al.* in 2002, and is showed in Table 3 [33].

The field of vision of the procedure is restricted, and it cannot evaluate distant mesorectal or inguinal lymph nodes. It only may be used to search for peri-rectal and/or promontory lymph nodes, described as uN+ when peri-rectal adenopathy 5–10 mm in diameter with malignancy features (round, hypoechoic, sharp contours) or more than 10 mm in diameter are observed [32].

EAUS and MRI are at present the 2 most accepted modalities for assessment of locoregional disease. EAUS determines primary tumor depth, perirectal lymph node and anal sphincter involvement. MRI also determines involvement of regional lymph node, other than perirectal. It seems that EAUS has an advantage over MRI in the evaluation of small tumors on the surface of the anal canal. For systemic staging CT of chest and abdomen is indicated.

There is limited data on defining the value of EAUS for locoregional staging. Even if EAUS seems to accurately determine the size and the depth of penetration into the sphincter complex and predicting local recurrence and patient survival, there is still a limited knowledge on the real accuracy, sensibility, and specificity of this technique. Probably due to the conservative treatment largely performed on these patients, without possibility to compare results with a histopathological specimen analysis.

There is only one study to date that directly compares EAUS (using two-dimensional imaging) with MRI in the primary staging of anal SCC [34], with comparable results in assessing primary tumor size and perirectal lymph node status. In this study by Otto *et al.* in 2009, 45 anal cancer patients were included, with the results of T staging and perirectal lymph node status evaluated by EAUS and MRI yielding high concordance (kappa index of 0.63 and 0.77 respectively). A correct identification of cancers as such, irrespective of the tumor extension and T stage, was made in all cases by EAUS (100% sensitivity) but in only 40 of 45 cases by MRI (88.9% sensitivity), and 4 of the 5 tumors which were missed by MRI were stage T1 cancers. They concluded that EAUS may be superior to MRI for detection of small superficial tumors. However, MRI is needed for N staging, because EAUS cannot detect other than perirectal lymph nodes.

The study by Giovanni *et al.* [35] compared the staging accuracy of EAUS with respect to the recurrence rate and survival in 115 patients. The better results were achieved by EAUS, with a significantly greater proportion of superficial lesions classified by EAUS, having a complete response to treatment than those classified by conventional TNM staging.

Also, Tarantino *et al.* in 2002 [33] investigated the suitability of EAUS for anal SCC staging in 12 patients. A surgical specimen was available as the gold standard in 5 patients, in whom the tumor was also 100% correctly identified by EAUS. They concluded that EAUS can accurately determine the depth of penetration of SCC into the sphincter complex and can be used to gauge accurately the response of these tumors to CRT. However, no comparison was made with MRI or other examination methods.

Table 3. Endoanal ultrasound staging for anal canal cancer [33].

Anal canal cancer - endoanal ultrasound staging	
uT1	Tumor invades mucosa and submucosa
uT2	Tumor invades the sphincter complex
uT2a	Tumor invades only the internal anal sphincter
uT2b	Tumor invades into the external anal sphincter
uT3	Tumor invades through the sphincter complex into the perianal tissue
uT4	Tumor invades adjacent structures

Endoanal ultrasound for anal cancer surveillance

Digital rectal examination is the mainstay of determining complete response after treatment. There are no formal recommendations with regard to post-CRT imaging techniques. Careful clinical inspection of the inguinal regions is also necessary. CT of chest, abdomen and pelvis is controversial or used in more advanced disease.

EAUS is controversial as oedema and scar tissue may be difficult to distinguish from persistent tumor, even with new techniques such as three dimensional EAUS. Although experienced examiners may be able to differentiate scar from recurrent disease, certain cases may prove to be difficult.

Some studies suggested that EAUS may have a role in surveillance of patients after successful treatment of the initial disease [28]. Follow-up with serial EAUS has gained popularity with some promising results [33, 36]. Martellucci *et al.* [36], enrolled 16 SCC patients treated with the same CRT regimen. Patients were examined pre- and after treatment, at least with 4 studies. Recurrence was found in 2 patients and none of the other 14 patients showed any evidence of residual tumors, although a normal anatomy of the sphincter complex was described for only 2 of them. For the remaining patients, EAUS showed abnormalities believed to represent radiation-induced changes rather than residual disease. To this end, the most useful information was provided by comparison of the consecutive follow-up EAUS with the first post CRT result.

Some investigators have defined that EAUS did not provide any advantage over digital rectal examination in identifying locally recurrent anal cancer. In a series of 82 patients with 14 recurrences [37] and another with 175 patients and 17 recurrences [38], all were detected by visual inspection and digital examination.

EAUS for guiding brachytherapy

A few centers have extended the application of 3D endoluminal ultrasound for guiding brachytherapy procedures in anal canal, with the advantages of optimizing implant procedure and better information for dose planning. There are currently limited data on the use of high-dose rate (HDR) brachytherapy in anal cancer and lack of consensus on the optimal fractionation schedule. Niehoff *et al.* have described their long term clinical experience with 3D EAUS in 104 patients with a 10-year mean follow-up period, showing a local control of 89% and overall survival of 93% [39].

References

1. Glynne-Jones R, Wyrwicz L, Tiret E, Brown G, Rodel C, Cervantes A, *et al.* Rectal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up Annals of Oncology 2017 Jul 1; 28 (Suppl 4): iv22–iv40.
2. Siegel RL, Miller KD, Jemal A. Cancer Statistics, 2018. CA Cancer J Clin. 2018 Jan;68 (1):7-30.
3. Bailey CE, Hu CY, You YN, Bednarski BK, Rodriguez-Bigas MA, Skibber JM, *et al.* Increasing disparities in the age-related incidences of colon and rectal cancers in the United States, 1975-2010. JAMA Surg.2015 Jan;150(1):17-22.
4. Uberoi AS, Bhutani MS. Has the role of EUS in rectal cancer staging changed in the last decade? Endosc Ultrasound. 2018;7(6):366-70.
5. Jessup JM, Goldberg RM, Aware EA, *et al.* Colon and Rectum. In: AJCC Cancer Staging Manual, 8th, Amin MB (Ed), AJCC, Chicago 2017. p.251.
6. Frasson M, Garcia-Granero E, Roda D, Flor-Lorente B, Roselló S, Esclapez P, *et al.* Preoperative chemoradiation may not always be needed for patients with T3 and T2N+ rectal cancer. Cancer. 2011 Jul 15;117(14):3118-25.
7. Gleeson FC, Clain JE, Papachristou GI, Rajan E, Topazian MD, Wang KK *et al.* Prospective assessment of EUS criteria for lymphadenopathy associated with rectal cancer. Gastrointest Endosc. 2009 Apr,69(4):896‐903.
8. Puli SR, Bechtold ML, Reddy JB, Choudhary A, Antillon MR, Brugge WR. How good is endoscopic ultrasound in differentiating various T stages of rectal cancer? Meta‐analysis and systematic review. Ann Surg Oncol. 2009 Feb;16(2):254‐65.
9. Lin. S, Luo G, Gao X, Shan H, Li Y, Zhang R, *et al.* Application of endoscopic sonography in preoperative staging of rectal cancer: six-year experience. J Ultrasound Med. 2011 Aug;30(8):1051-7.
10. Gao Y, Hu JL, Zhang XX, Zhang MS, Zheng XF, Liu SS, *et al.* Accuracy of endoscopic ultrasound in rectal cancer and its use in transanal endoscopic microsurgery. Minim Invasive Ther Allied Technol. 2019 Mar 8:1-8.
11. Marusch F, Ptok H, Sahm M, Schmidt U, Ridwelski K, Gastinger I, *et al.* Endorectal ultrasound in rectal carcinoma - do the literature results really correspond to the realities of routine clinical care? Endoscopy. 2011 May;43(5):425-31.
12. Ashraf S, Hompes R, Slater A, Lindsey I, Bach S, Mortensen NJ, *et al.* A critical appraisal of endorectal ultrasound and transanal endoscopic microsurgery and decision-making in early rectal cancer. Colorectal Dis. 2012 Jul;14(7):821-6.
13. National Comprehensive Cancer Network. Rectal Cancer (Version 1.2019 – March 15,2019). https://www.nccn.org/professionals/physician_gls/pdf/rectal.pdf.
14. Morino M; Risio M; Bach S; Beets-Tan R; Bujko K; Panis Y, et al. Early rectal cancer: the European Association for Endoscopic Surgery (EAES) clinical consensus conference. Surg Endosc. 2015 Apr;29(4):755-73.
15. Puli SR, Reddy JB, Bechtold ML, Choudhary A, Antillon MR, Brugge WR. Accuracy of endoscopic ultrasound to diagnose nodal invasion by rectal cancers: a meta‐analysis and systematic review. Ann Surg Oncol. 2009 May;16(5):1255-65.
16. Bipat S, Glas AS, Slors FJ, Zwindderman AH, Bossuyt PM, Stoker J. Rectal cancer: local staging and assessment of lymph node involvement with endoluminal US, CT, and MR imaging: a meta-analysis. Radiology. 2004 Sep;232(3):773-83.
17. Mulla M, Deb R, Singh R. MRI in T staging of rectal cancer: How effective is it? Indian J Radiol Imaging. 2010 May;20(2):118‐21.
18. Burdan F, Sudol-Szopinska I, Staroslawska E, Kolodziejcza KM, Klepacz R, Mocarska A, *et al.* Magnetic resonance imaging and endorectal ultrasound for diagnosis of rectal lesions. Eur J Med Res. 2015 Jan; 20: 4.
19. Evans J, Patel U, Brown G. Rectal cancer: primary staging and assessment after chemoradiotherapy. Semin Radiat Oncol. 2011 Jul;21(3): 169–177.
20. Marone P, de Bellis M, Avallone A, Delrio P, di Nardo G, D'Angelo V, *et al.* Accuracy of endoscopic ultrasound in staging and restaging patients with locally advanced rectal cancer undergoing neoadjuvant chemoradiation. Clin Res Hepatol Gastroenterol. 2011 Oct;35(10):666-70.
21. Memon S, Lynch AC, Bressel M, Wise AG, Heriot AG. Systematic review and meta-analysis of the accuracy of MRI and endorectal ultrasound in the restaging and response assessment of rectal cancer following neoadjuvant therapy. Colorectal Dis. 2015 Sep;17(9):748-61.
22. Gleeson FC, Larson DW, Dozois EJ, Boardman LA, Clain JE, Rajan E, *et al.* Local recurrence detection following transanal excision facilitated by EUS-FNA. Hepatogastroenterology. 2012 Jun;59(116):1102-7.
23. Kahi CJ, Boland CR, Dominitz JA, Giardiello FM, Johnson DA, Kaltenbach T, *et al.* Colonoscopy surveillance after colorectal cancer resection: recommendations of the US multi-society task force on colorectal cancer. Am J Gastroenterol. 2016 Mar;111(3):337-46.

24. Glynne-Jones R, Nilsson PJ, Aschele C, Goh V, Peiffert D, Cervantes A, *et al.* Anal cancer: ESMOESSO- ESTRO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 2014; 25 (Suppl 3): 10–20.
25. Fenger C, Frisch M, Marti MC, Parc R. Tumours of the anal canal. In: Hamilton SR, Aaltonen LA (eds.): WHO classification of tumours, Volume 2: Pathology and genetics. Tumours of the digestive System. Lyon: IARC Press 2000; 145–55.
26. National Comprehensive Cancer Network. Anal Carcinoma (Version 1.2019 – March 15,2019) https://www.nccn.org/professionals/physician_gls/pdf/anal.pdf
27. Giani I, Mistrangelo M, Fucini C; Italian Society of Colo-Rectal Surgery. The treatment of squamous anal carcinoma: guidelines of the Italian Society of Colo-Rectal Surgery. Tech Coloproctol. 2013 Apr;17(2):171-9.
28. Stewart DB, Gaertner WB, Glasgow SC, Herzig DO, Feingold D, Steele SR. The American Society of Colon and Rectal Surgeons Clinical Practice Guidelines for Anal Squamous Cell Cancers (Revised 2018). Dis Colon Rectum. 2018 Jul;61(7):755-774.
29. Darragh TM, Colgan TJ, Cox JT, Heller DS, Henry MR, Luff RD, *et al.* The Lower Anogenital Squamous Terminology standardization project for HPV-associated lesions: background and consensus recommendations from the College of American Pathologists and the American Society for Colposcopy and Cervical Pathology. Arch Pathol Lab Med. 2012 Oct;136(10):1266-97.
30. Welton ML, Steele SR, Goodman KA, *et al.* Anus. In: AJCC Cancer Staging Manual, 8th ed, Amin MB (Ed), AJCC, Chicago 2017. p.275.
31. Nielsen A, Munk C, Kjaer SK. Trends in incidence of anal cancer and high-grade anal intraepithelial neoplasia in Denmark, 1978-2008. Int J Cancer. 2012 Mar 1;130(5):1168-73.
32. Moureau-Zabotto L, Vendrely V, Abramowitz L, Borg C, Francois E, Goere D, *et al.* Anal cancer: French Intergroup Clinical Practice Guidelines for diagnosis, treatment and follow-up (SNFGE, FFCD, GERCOR, UNICANCER, SFCD, SFED, SFRO, SNFCP). Dig Liver Dis. 2017 Aug;49(8):831-840.
33. Tarantino D, Bernstein MA. Endoanal ultrasound in the staging and management of squamous-cell carcinoma of the anal canal: potential implications of a new ultrasound staging system. Dis Colon Rectum. 2002 Jan;45(1):16-22.
34. Otto SD, Lee L, Buhr HJ, Frericks B, Höcht S, Kroesen AJ. Staging anal cancer: prospective comparison of transanal endoscopic ultrasound and magnetic resonance imaging. J Gastrointest Surg. 2009 Jul;13(7):1292-8.
35. Giovannini M, Bardou VJ, Barclay R, Palazzo L, Roseau G, Helbert T, *et al.* Anal carcinoma: prognostic value of endorectal ultrasound (ERUS) - results of a prospective multicenter study. Endoscopy. 2001 Mar;33(3):231-6.
36. Martellucci J, Naldini G, Colosimo C, Cionini L, Rossi M. Accuracy of endoanal ultrasound in the follow-up assessment for squamous cell carcinoma of the anal canal treated with radiochemotherapy. Surg Endosc. 2009 May;23(5):1054-7.
37. Lund JA, Sundstrom SH, Haaverstad R, Wibe A, Svinsaas M, Myrvold HE.:Endoanal ultrasound is of little value in follow-up of anal carcinomas.Dis Colon Rectum. 2004 Jun;47(6):839-42.
38. Peterson CY, Weiser MR, Paty PB, Guillem JG, Nash GM, Garcia-Aguilar J, *et al.* Does endoscopic ultrasound improve detection of locally recurrent anal squamous-cell cancer? Dis Colon Rectum. 2015 Feb; 58(2):193-8.
39. Niehoff P, Schumacher N, Siebert FA, Doniec JM, Kimmig B, Kovacs G, et al. PO-1040: TRUS guided interstitial HDR Brachytherapy combined with RCT for treatment of anal cancer. Radiother Oncol. 2014;111(suppl1):S160.

7

Endoscopic Ultrasound-Elastography and Contrast-Enhanced Endoscopic Ultrasound

Richard Azevedo, Ana Caldeira

KEY POINTS

EUS-ELASTOGRAPHY (EUS-E)

- EUS-E is an emerging noninvasive technique that can add some diagnostic value to conventional EUS in the evaluation of focal pancreatic lesions.
- Strain EUS-E can be applied as a qualitative and a semi-quantitative technique.
- In case of a strong clinical suspicion of pancreatic cancer with a negative/inconclusive FNA, a hard focal lesion on EUS-E and/or hypovascular lesion on CE-EUS should lead to FNA repetition or referral to surgery.
- Currently, EUS-E cannot be recommended for differentiating advanced chronic pancreatitis from PDAC.
- Strain EUS-E can help to discriminate between benign and malignant lymph nodes and may help in targeting the most suspicious nodule for malignant invasion, in order to perform FNA.
- The use of EUS-E for characterization of subepithelial lesions still needs more data to be systematically applied in clinical practice.
- EUS-E for rectal cancer staging is still under investigation and further studies are needed.

CONTRAST-ENHANCED ENDOSCOPIC ULTRASOUND (CE-EUS)

- Pancreatic cystic lesions with mural nodules on standard EUS should be further evaluated by CE-EUS. Hyperenhancement pattern of mural nodules, solid masses or septations should raise awareness towards malignant transformation and EUS-FNA should be considered.
- CEH-EUS is helpful in the characterization of small (≤20 mm) solid pancreatic lesions and can be used to differentiate between PDAC and P-NET.
- Concomitant use of both EUS-FNA and CEH-EUS increases the diagnostic yield and accuracy of FNA.
- The combination of CE-EUS and EUS-E to differentiate between benign and malignant solid pancreatic lesions does not seem to increase diagnostic yield of either technique in separate.
- PDAC typically presents as a hypoenhancing lesion on CE-EUS: in these cases, a negative cytology should not be considered as benign and FNA repetition is mandatory.
- CE-EUS is not recommended for routine discrimination of benign from malignant lymph nodes.
- CE-EUS may accurately differentiate between GIST and leyomioma.

Endoscopic ultrasound-elastography

Basic principles

Real-time Endoscopic Ultrasound-Elastography (EUS-E) is an emerging noninvasive sonographic modality that provides images and measurements related to tissue stiffness [1]. It can be used in combination with conventional EUS, with the potential for improving the accuracy of this technique [2,3].

Two different elastographic techniques have been developed: the strain technique and the shear wave technique, but only the former is available for EUS examinations (for both radial and linear echoendoscopes) [1].

Strain Elastography (SE) is both a qualitative and semi-quantitative method that measures compression-induced tissues deformations ("strains") within a selected region of interest (ROI). The ROI is manually selected and should include both the entire pathological tissue under investigation (whenever possible) and also "normal" surrounding tissue as a reference [4]. According to the available literature, the best image quality is obtained when the pathological area covers 25-50% of the ROI [5].

EUS-E detects small deformations caused by tissue compression and grades the degree of relative strain between the ROI included tissues on a scale of 1 to 255; each value will correspond to a different shade from a color spectrum. As so, the tissues strains are visualized using a transparent color overlay on the B-mode image [4]. Different colors are used to illustrate differences between stiffness of tissues included in the ROI. Most systems use a red-green-blue color map, in which stiffer tissue areas are displayed in dark blue to blue, whereas softer tissues are shown in green to red spectrum [4]. Stiffer tissues have lower strains (which means that deform less under compression), compared to softer tissues, which have higher strains.

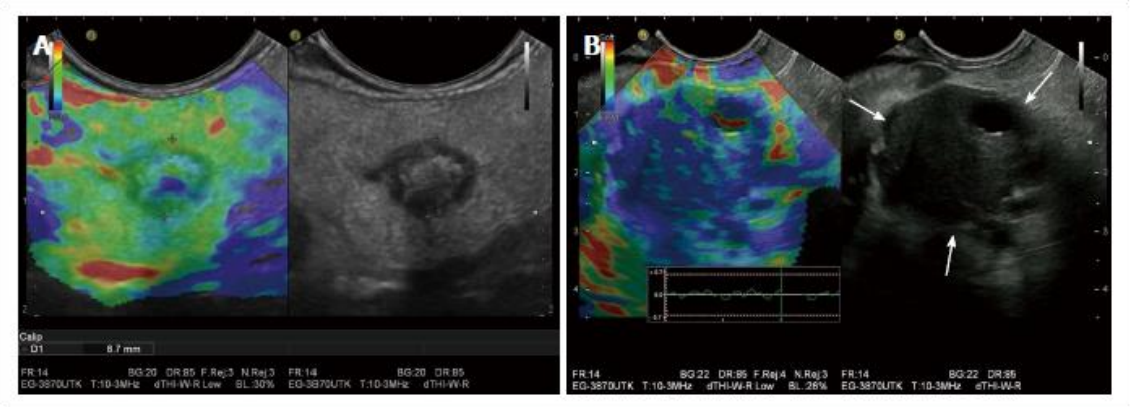

Figure 1: Benign and malignant pancreatic lesions on EUS-E:

A: A benign lesion (pancreatic teratoma) showing a soft green pattern
B: A pancreatic ductal adenocarcinoma showing a blue (stiffer) pattern. Adapted from Cui XW *et al.* [1]

By manipulating the echoendoscope, the internal physiological pulsations from cardiac or respiratory contractions create the required pressure and extra compression is seldom needed to produce an elastographical image [4]. Below the color image produced, a strain graph provides feedback to the operator on the degree and uniformity of the compression technique. In the freeze mode, the strain graph can be useful to select the most relevant frames for analysis – ideally a sine curve with values between 0.1-1% on the Y-axis (the scale of % strain) should be selected for further analysis (Fig. 2).

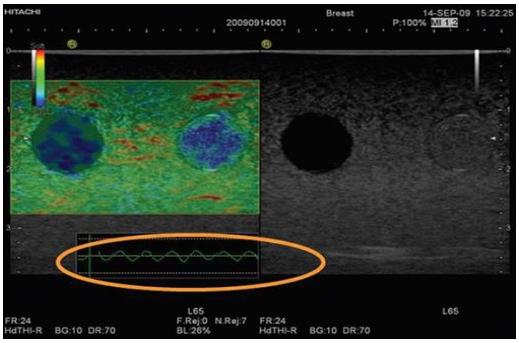

Figure 2:
Quality parameters – the strain graph display.
Adapted from Dietrich *et al.* [4]

Usually, qualitative analysis includes a five-step score method based on the predominant color pattern of the potential pathological area: homogenously hard (homogenously blue), heterogeneously hard (predominantly blue but with some heterogeneity), heterogeneously soft (predominantly green but with some heterogeneity) or homogenously soft (homogenously green) [1,6,7].

In order to overcome subjectivity and inter-observer variability of qualitative analysis [8,9], two semi-quantitative techniques have been introduced, to improve the accuracy and reproducibility of the method [4]:

Strain Ratio (SR) measures the relative strain between two selected areas within a ROI and is useful for measuring the relative stiffness of a discrete mass lesion. The operator selects two non-overlapping areas (usually area A is the lesion/pathological tissue and area B is the reference "normal" tissue) and the tissue stiffness is expressed as a relative ratio – SR represents the B/A quotient [1,4,10] (Fig. 3).

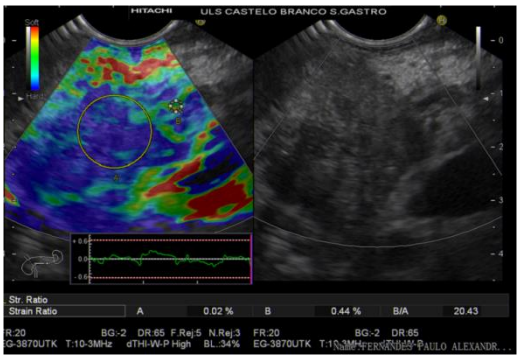

Figure 3: Strain Ratio applied to the pancreas.

Strain Histogram (SH) calculates the strain values of elemental tissue areas within the ROI and its distribution is displayed as a histogram (Gaussian distribution curve), from which several parameters can be derived for quantitative evaluation. It is useful for diffuse diseases, such as chronic hepatitis and pancreatitis [1,4] (Fig. 4).

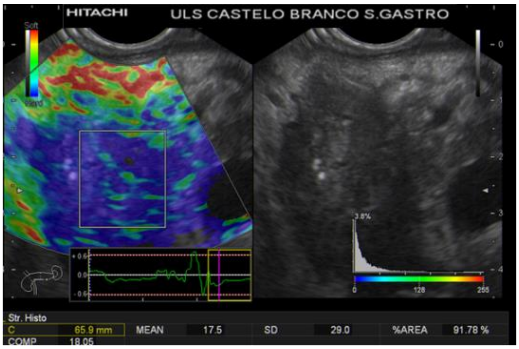

Figure 4: Strain histogram applied to the pancreas.

Clinical applications

EUS-E is only used in the assessment of solid lesions; as so, cystic lesions and solid lesions with cystic components are usually shown as artifacts and should not be evaluated by EUS-E [1,11,12]. Current clinical indications for EUS-E assessment are mainly solid pancreatic lesions, submucosal GI masses, lymph nodes, focal left liver lesions and left adrenal lesions [1].

One of the advantages of real-time EUS-E is the ability to assess the elasticity of lesions in locations only accessible from de gastrointestinal tract (such as pancreatic masses and mediastinal and abdominal lymph nodes), thus improving the diagnostic yield of the examination [1].

It should be clarified that EUS-E is not a modality that can replace Fine Needle Aspiration (FNA) but can be a complement to the standard EUS examinations, due to its noninvasiveness, ease of use and low cost [4].

Intrinsic limitations of EUS-E include the difficulty of controlling tissue compression by the echoendoscope, the motion artifacts secondary to respiratory and heart movements and the difficulty in excluding nearby structures from the ROI (heart, major vessels or spine) [13]. A stable elastographic image for at least 5 seconds and the mean of 3 measurements for SR can partly avoid these limitations [13].

Elastographic features of some tissues still remain unclear [14]. The available EUS-E techniques do not allow to assess tissues in a fully quantitative manner and ultimately always rely on subjective evaluation of the operator [14].

Pancreas

Elastographically, a normal and young pancreas shows a homogenously soft (green) pattern [1,4] and malignant lesions are usually harder than adjacent healthy pancreatic tissue. Several meta-analysis (combining qualitative and semi-quantitative EUS studies) have shown that EUS-E is a reliable technique for differentiating solid pancreatic masses, with a sensitivity ranging from 95-97% and a specificity between 67-76% [1,15, 16,17].

Qualitative analysis

On EUS-E examination, pancreatic ductal adenocarcinoma (PDAC) shows an almost unequivocally stiffer pattern than the adjacent normal parenchyma, due to the presence of fibrosis and desmoplasia [1,6,9]. – it can be excluded with a negative predictive value >95% when a homogeneously green pattern is seen [18].

Two different classifications for color patterns on pancreas examination have been created and applied. A five score classification has shown an overall accuracy for diagnosing malignancy of 90% in a multicenter study [12] (Table 1); a four score classification (Table 2) has shown an overall accuracy for malignancy of 100% [19]. However, these promising results have to be confronted with disappointing results from 2 other studies, showing significantly lower accuracy for diagnosing malignancy (45%) [7] and highlighting the limitation of qualitative EUS-E to differentiate between malignant tumors and chronic pancreatitis, probably due to their similar fibrous pattern [6]. As so, the diagnostic accuracy of qualitative EUS-E is variable among the published studies, probably due to the subjective analysis and interpretation of the elastographic color pattern [1].

Table 1: Five score classification system for EUS-E. Adapted from Cui XW *et al.* [1]

Score	Color pattern	Stiffness	Histology
1	Green	Homogeneous soft	Normal pancreatic tissue
2	Green, yellow and red	Soft heterogeneity	Fibrosis
3	Mostly blue with minimal heterogeneity	Hard	Early pancreatic adenocarcinoma
4	Central green hypoechoic region and blue tissue outer layer	Hard	Neuroendocrine tumor, metastasis
5	Blue lesions with heterogeneity due to necrosis	Hard	Advanced pancreatic adenocarcinoma

Table 2: Four score classification system for EUS-E. Adapted from Cui XW *et al.* [1]

Score	Color pattern	Stiffness	Histology
1	Homogeneous green	Soft	Normal pancreas
2	Heterogeneous, green-predominant	Soft	Inflammatory pancreatic masses
3	Heterogeneous, blue-predominant	Hard	Pancreatic malignant tumors
4	Homogeneous blue	Hard	Pancreatic neuroendocrine malignant lesions

Semi-quantitative analysis

Available literature reports similar accuracy for both SR and SH in differentiating between benign and malignant pancreatic masses [20].

Iglesias-Garcia *et al.* [13] showed that semi-quantitative EUS-E with SR yields an overall diagnostic accuracy for malignancy of 97.7%, when SR level was >6.04. However, the cutoff values of the SR to predict malignancy vary widely between different studies (ranging from 3.7 to 24) [21-26], highlighting the actual lack of standardization of the technique [27].

Iglesias-Garcia *et al.* [22] also demonstrated a perfect correlation between SR and SH for diagnosing pancreatic malignancy when SR >10 and SH <50 cutoff values were used, with an overall diagnostic accuracy reaching 98.4%. Other studies reported an overall diagnostic accuracy for malignancy ranging from 85-89%, when a cutoff value of 175 for SH was used [28,29].

Lymph nodes

Differentiating between benign and malignant lymph nodes (LN) is essential for tumor staging, prognosis assessment and for selection of the most suitable treatment option for many cancers, such as esophageal, gastric, bronchial and pancreatic carcinomas [3].

Despite some established EUS-patterns that point towards malignant LN (hypoechoic structure, round shape, sharp margins and >10 mm diameter), diagnostic accuracy of EUS varies between 50-100% [30] and this is still a challenge for the ultrasonographer [1], particularly for small malignant nodes at early stages that may lack the mentioned features [31]. In this scenario, EUS-E has potential to add some diagnostic value to B-mode EUS, helping to differentiate between benign and malignant LN or by better targeting lymph nodes for EUS-guided FNA [32-34].

Qualitative analysis

A meta-analysis showed a pooled sensitivity of 88% and a specificity of 85% of qualitative EUS-E to differentiate between benign and malignant lymph nodes [35], pointing out that EUS-E is a valuable non-invasive technique in this specific scenario.

Semi-quantitative analysis

A prospective study using SH to evaluate 76 cervical, mediastinal, or abdominal lymph nodes, showed that for a cutoff value of 166 for the SH, the overall accuracy to detect malignant LN was 88.5% [36]. Another prospective study using SR for the evaluation of esophageal LN, in the context of esophageal cancer staging, showed better accuracy of EUS-E as compared to conventional EUS criteria in diagnosing malignant LN (83% sensitivity, 96% specificity, 95% positive

predictive value, 86% negative predictive value and 90% of overall accuracy for a cutoff value of SR ≥7.5) [34].

EUS-E can be helpful to identify focal stiffer malignant infiltration in LN by differentiated carcinomas [37-40]. It means that EUS-E has the ability to better identify the most inconspicuous metastatic changes in terms of tissue deformation and so can better guide EUS-FNA by targeting the most suspicious regions within the LN [41].

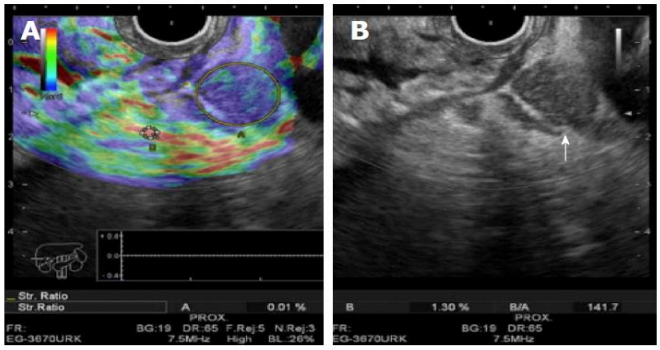

Figure 5: Evaluation of a gastric lymph node in the context of gastric tumor staging.
A: Qualitative elastography shows a blue-predominant lesion, suggestive of malignancy.
B: On B-mode EUS a round and sharply demarcated LN is seen (white arrow). Adapted from Valero M *et al.* [42]

Gastrointestinal wall lesions

Initial reports demonstrate a promising role for the evaluation and staging of gastrointestinal wall lesions. However, its clinical significance is not yet established [30].

Concerning subepithelial lesions, EUS-E can provide additional information on tissue stiffness, which may help to increase the accuracy of the diagnosis and staging, but, for the time being, few reports concerning this potentiality have been published [43,44].

On EUS-E, benign subepithelial lesions usually show an intermediate stiffness with homogenous strain pattern [45,43]. However, degenerative changes may hamper the diagnosis of benignity. Lipomas, the most common subepithelial lesions, usually present a homogenously soft (green) pattern but harder lipomas may also be found [1]. Gastrointestinal Stromal Tumors (GISTs) typically show a homogeneously stiff (blue) pattern, but these lesions are difficult to evaluate using EUS-E, as this technique does not provide enough resolution to properly identify microfoci usually found in these tumors [1].

Further studies are needed to better define the role of EUS-E in this scenario.

Rectal cancer

Available literature suggests that the addition of SR elastography to transrectal US may play a role in differentiating colorectal adenomas from adenocarcinomas, with high accuracy levels for a SR cutoff value of 1.25 [46,47].

Besides that, SR elastography showed better accuracy when compared to standard transrectal US and MRI examinations; as so, it seems that transrectal elastography can add some value to standard US staging of rectal adenomas and early cancers, allowing more suitable selection of patients eligible for local resection [46]. Despite these promising results, more research studies are needed to confirm these initial findings. Besides that, reports on the use of EUS-E for colorectal lesions are lacking; further studies are needed in this field.

Contrast-enhanced endoscopic ultrasound

Basic principles

Contrast-Enhanced Endoscopic Ultrasound (CE-EUS) is an image modality used to evaluate the blood flow pattern inside a tissue [48], and has shown to be an accurate method to assess vascularization of tumoral lesions, helping in the differential diagnosis between benign and malignant [48].

For this purpose, an Ultrasonographic Contrast Agent (UCA), corresponding to gas-filled microbubbles stabilized by a lipid or protein shell, is used. These microbubbles are smaller than erythrocytes and do not diffuse out of the capillary bed, allowing a real time perfusion imaging characterization of both the macrovasculature and microvasculature [49,50].

Two different techniques are available:

Contrast–Enhanced Doppler EUS (CED-EUS), in which the intensity of the Doppler signal (color or power Doppler) is enhanced by UCA. It uses a high mechanical index (MI)~~,~~ leading to artifacts caused by tissue motion and microbubble destruction [50].

Contrast-Enhanced Harmonic EUS (CEH-EUS), established as an evidence based technique and most commonly used, in which low MI allow the visualization of blood flow in small vessels [50].

Sonovue® (sulfur hexafluoride with a phospholipid shell) is a second generation UCA agent used in Europe. A bolus of 4.8 mL of Sonovue® is administered through a 21-gauge peripheral intravenous cannula, followed by a 5-mL saline flush. Real-time CE-EUS is then performed using contrast specific software, set for a low MI (0.08-0.3) to avoid microbubble disruption [50]. After UCA injection, the lesion(s) are scanned continuously until the enhancement effect begins to subside. The overall degree of enhancement (nonenhancing/ hypoenhancing/ isoenhancing/ hyperenhancing) and pattern of distribution (inhomogeneous/homogeneous) of the UCA is assessed in each vascular phase [51]:

-The Arterial phase, starting from 10–20 seconds after bolus injection to approximately 30–45 seconds later – the “wash-in” phase

-The Venous phase, starting 30–45 seconds later – the “wash-out” phase.

Besides standard CE-EUS, a Dynamic CE-EUS, using appropriate software for contrast signal quantification after UCA injection, can be performed.

The intensity of contrast signal can be quantified by calculation of the time-intensity curve (TIC): time-related intensity values of the wash-in and wash-out phases, fitting the values based on mathematical models. Several parameters can be extracted from TIC analysis (peak intensity, time to peak intensity, wash-in and wash-out rate and area under the curve) that quantitatively describe the perfusion characteristics in a region of interest [50]. However, the exact role of this EUS modality is still under investigations and further studies are needed.

Sonovue® has an excellent safety and tolerance profile and multiple separate boluses can be given to evaluate multiple lesions. CE-EUS is a rapid, noninvasive, cost-effective (relatively inexpensive compared to CT/MRI) and simple diagnostic procedure which can be performed at the patient’s bedside, immediately after detection of a lesion by baseline EUS.

Clinical applications

Pancreas – solid lesions

Published meta-analysis [52,53] have shown that CE-EUS is a useful tool for the differential diagnosis of Pancreatic Ductal Adenocarcinoma (PDAC), reporting a more accurate EUS characterization of solid pancreatic lesions after UCA administration [49]. PDAC typically presents as a heterogeneous hypoenhancing lesion in all phases of CE-EUS [50,54], whereas Pancreatic Neuroendocrine Tumors (P-NET), lymphoma, pancreatic metastasis, serous microcystic cystadenoma and pseudo-papillary tumors show an iso- or hyper-enhancing pattern after UCA administration [49,50,55]. A hyperenhancement pattern with slow washout is a typical feature of P-NETs, while filling defects and lack of venous vessels are highly predictive of malignancy [56].

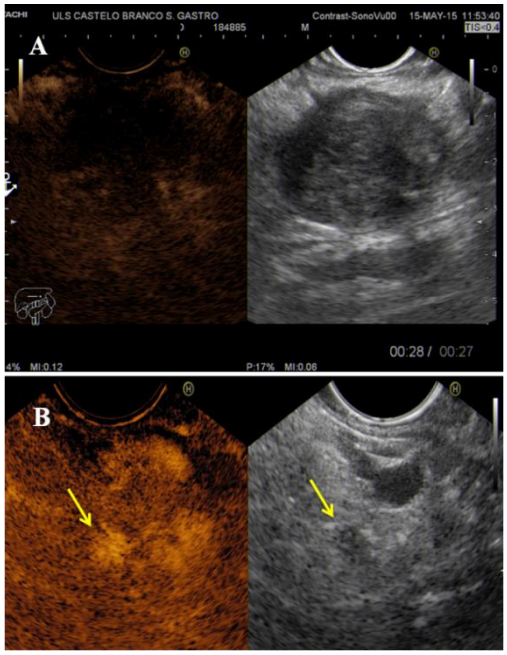

Figure 6: Conventional (left panel) and CE-EUS (right panel) images of pancreatic tumor.
A: A PDAC with the typical hypoenhancement pattern; **B:** A pNET (hyperenhancement pattern).

It is important to note that most of the mass forming focal pancreatitis also show an iso- or hyper- enhancing pattern on CE-EUS [57,58], exhibiting a netlike regular vascularization, while focal and diffuse autoimmune pancreatitis shows a hyperenhancement pattern [50].

Meta-analysis reported a pooled sensitivity of 4% and a specificity of 89% of CE-EUS for diagnosing PDAC vs. non-PDAC [59,60]. One study found that the presence of a hyperenhancing solid pancreatic lesion on CE-EUS was highly specific (>98%) for excluding PDAC, while a hypoenhancing lesion was highly sensitive (>86%) for its diagnosis [61]. This hypoenhancing pattern has shown to have a high diagnostic value for the detection of solid pancreatic masses ≤20 mm [61].

CEH-EUS is the most commonly used technique for the differentiation of PDAC from other solid pancreatic lesions.

Also, the dynamic quantification of intensity of contrast signal through TIC analysis has shown promising results in the diagnosis of PDAC [58]: the peak intensity may be helpful to differentiate between chronic pancreatitis and PDAC [62,63].

CE-EUS has also the potential to help targeting FNA: despite PDAC is usually seen as an

inhomogeneous hypoenhancing lesion, nonenhancing areas are thought to correspond to fibrosis or necrosis [64]. As so, improving accuracy and diagnostic yield of FNA by avoiding these areas and selecting the most adequate target is another advantage of CE-EUS [50,49,64]. A randomized trial found that performing CE-EUS before FNA of suspected PDAC was associated to fewer needle passes required to obtain samples, as compared to conventional EUS-FNA [64].

Following the same principles, Dynamic CE-EUS could also be used to better target FNA [63].
The use of CEH-EUS for staging PDAC may increase the accuracy of tumor staging and the assessment of ressecability for biliary-pancreatic malignancies [65-66].

Concerning the differential diagnosis of benignity/malignancy of solid pancreatic tumors, the combination of EUS-E and CE-EUS does not seem to significantly increase the diagnostic accuracy of either technique performed alone [67]. In this study, EUS-E was able to differentiate between benign and malignant pancreatic lesions with a higher accuracy compared to CE-EUS and a possible additional value of CE-EUS could be to further characterize the type of malignant lesion [67]. As so, the complementary information given by the combination of both techniques, despite useful, does not translate into an increased diagnostic yield for malignancy. Further studies are needed to corroborate these statements.

Pancreas – cystic lesions

The diagnosis of incidental pancreatic cystic lesions (PCL) is increasing in the general population because of the routine use of cross-sectional imaging modalities [68]. It poses a major clinical dilemma, as the differential diagnosis spectrum is quite broad ranging from benign to malignant conditions [69].

Current imaging modalities, including EUS and EUS-FNA, have shown suboptimal accuracy in differentiating between different types of PCLs and in detecting malignancy [48], and available data for EUS-based differential diagnosis between benign and malignant lesions are conflicting [70].

Theoretically, neoplastic solid components should exhibit some signs of vascularization, as opposed to debris and mucus that are expected to be completely avascular [69].

CE-EUS may help in the diagnosis of PCL by enabling assessment of vascularization of structures like cyst walls, septa or mural nodules, and the discrimination of hyperenhancing mural nodules (protrusion of the cystic wall with contrast enhancement) from nonenhancing mucus clots (internal solid component without contrast enhancement) [71].
CE-EUS appears to be more accurate than standard EUS and CT-scan for the identification of mural nodules [48,72] and inter-observer agreement is moderate for Sonovue® [73]. Characterization of mural nodules by CE-EUS - morphology, height and degree of enhancement – has shown to be useful for risk stratification [68].
Therefore, the most recent European Guidelines [72] state that CE-EUS should be performed for further evaluation of mural nodules and also consider that it can also be helpful to assess vascularity within the cyst and septations. The presence of a hyperenhancement pattern of a mural nodule, solid mass or septations on CE-EUS evaluation points towards malignant transformation and EUS-FNA of the PCL should be considered [72].

FNA of mural nodules should be precisely targeted according to the CE-EUS findings in order to improve diagnostic yield, avoiding puncture of mucus plugs or debris [69].

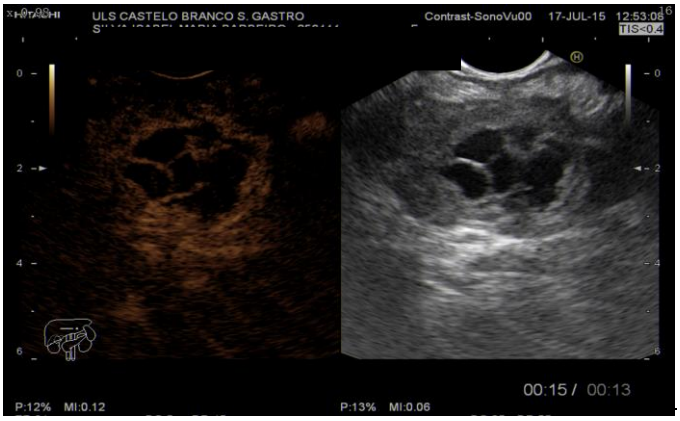

Figure 7: Pancreatic cystic lesion evaluated through CE-EUS – a solid component with hyperenhancing pattern (mural nodules) and a nonenhancing solid component (mucus) are seen.
Histology revealed a mucinous cystic neoplasm with high grade dysplasia.

Lymph nodes

A primary discrimination of LN could be helpful to increase diagnostic yield of FNA, mainly in cases of multiple and hard to reach enlarged LN [74].

Concerning malignant lymph nodes, and considering that the capillary bed of a metastatic lymph node is destroyed, the predicted behavior on CE-EUS would be of a hypoenhancing effect within the whole or just in certain areas of the LN [75,76], whereas the majority of benign lymph nodes demonstrate homogeneous enhancement. However, some conditions may hamper this clinical application of CE-EUS:

-First, lymphoma LN, despite malignant, are well vascularized within the capillary bed and cannot be distinguished from benign LN;
-Second, benign LN can have some necrotic areas, being erroneously interpreted as malignant LN;
-Third, there is always the possibility that cancer cell nests are overlooked on CE-EUS examination because of its small size.

For all the above mentioned reasons, the EFSUMB guidelines do not recommend the routine use of CE-EUS for LN differential diagnosis of malignancy [50,74]. Like EUS-E, it could be useful for FNA targeting; however, the beneficial effect seems to be minor [74].

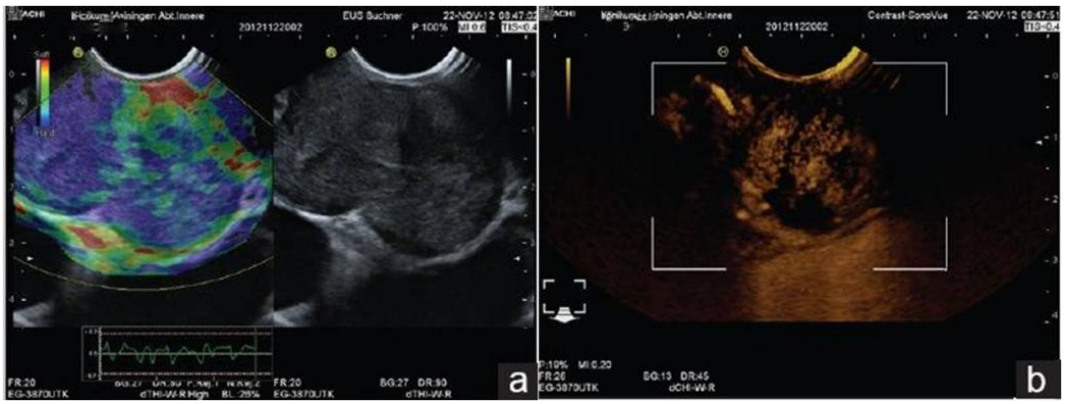

Figure 8: Typical malignant LN in the mediastinum of a patient with lung squamous cell carcinoma.
A: EUS-E shows blue (stiff) areas within the LN, suggestive of malignant infiltration. **B:** CEH-EUS with Sonovue® shows a hypoenhancing effect in some areas of the LN, suggesting also malignant infiltration.
Adapted from Hocke M *et al.* [74]

Gastrointestinal wall lesions

Concerning gastric subepithelial lesions, available literature has shown the usefulness of CE-EUS for accurately differentiate between GIST and leyomioma: hyperenhancement and avascular areas are seen in a high percentage of GISTs but not in leiomyoma [77]; detection of irregular intratumoral vessels in the arterial phase and a heterogeneous enhancement pattern are highly predictive for intermediate or high-risk GIST [50].

Besides that, dynamic CE-EUS with TIC analysis revealed that peak intensity in GISTs was significantly higher than that in benign tumors such as lipomas [78].

Assessment of tumor response to therapy

The emergence of novel therapies targeting tumor angiogenesis poses the need for new accurate and reproducible quantitative techniques to assess early changes in tumor vascularization [79]. In this context, Dynamic CE-EUS with TIC analysis may be useful to assess the grade of the tumor before therapy through the evaluation of tumor perfusion status [48].

Chemotherapy-induced changes in tumor vascularization may be a predictor of a successful tumor ablation [48] and may be assessed through CE-EUS: one study has shown a change in size and vascularity of gastric tumors during the chemotherapy cycle using CE-EUS [80]. As so, CEH-EUS allows the assessment of treatment induced changes of tumor vascularity in gastric cancer [50].

Another potential emerging role for CE-EUS would be a better characterization and prognostic assessment of rectal cancer [14] through the evaluation of tumor vascularization and response to angiogenic therapy. However, only limited studies concerning the application of CE-US on rectal cancer have been published [81,82]. So far, the lack of studies does not allow dragging any recommendation concerning this field [14,83]. In the near future, these principles of tumor vascular modification might be used for the evaluation of therapy of several digestive tract cancers, such as esophagus, stomach and rectal cancers [48].

Concerning EUS-guided local ablation of pancreatic tumors, dynamic CE-EUS can provide valuable information both of pre- and post-treatment assessment of tumor vascularization and perfusion, as shown in small pilot studies [84,85].

Despite promising results, further studies are needed to validate the usefulness of CE-EUS in this specific area of interest.

References

1. Cui XW, Chang JM, Kan QC, Chiorean L, Ignee A, Dietrich CF. Endoscopic ultrasound elastography: Current status and future perspectives. World J Gastroenterol. 2015; Dec 21(47):13212-13224.
2. Kekelidze M, D'Errico L, Pansini M, Tyndall A, Hohmann J. Colorectal cancer: current imaging methods and future perspectives for the diagnosis, staging and therapeutic response evaluation. World J Gastroenterol. 2013 Dec 14 ;19(46):8502-8514.
3. Ravikanth R. Applications of Endoscopic Ultrasound-Elastography. J Med Ultrasound. 2018 Apr-Jun;26(2):111-112.
4. Dietrich CF, Bibby E, Jenssen C, Saftoiu A, Iglesias-Garcia J, Havre RF. EUS elastography: How to do it? Endosc ultrasound. 2018 Jan-Feb;7(1):20-28.
5. Havre RF, Elde E, Gilja OH, Odegaard S, Eide GE, Matre K, *et al.* Freehand real-time elastography: impact of scanning parameters on image quality and in vitro intra- and interobserver validations. Ultrasound Med Biol. 2008 Oct;34(10):1638-1650.
6. Janssen J, Schlorer E, Greiner L. EUS elastography of the pancreas: feasibility and pattern description of the normal pancreas, chronic pancreatitis, and focal pancreatic lesions. Gastrointest Endosc. 2007 Jun;65(7):971-978.
7. Hirche TO, Ignee A, Barreiros AP, Schreiber-Dietrich D, Jungblut S, Ott M, *et al.* Indications and limitations of endoscopic ultrasound elastography for evaluation of focal pancreatic lesions. Endoscopy. 2008;Nov 40(11):910-917.
8. Chiorean L, Barr RG, Braden B, Jenssen C, Cui XW, Hocke M, *et al.* Transcutaneous ultrasound: elastographic lymph node evaluation. current clinical applications and literature review. Ultrasound Med Biol. 2016 Jan;42(1):16-30.
9. Dietrich CF, Barr RG, Farrokh A, Dighe M, Hocke M, Jenssen C, *et al.* Strain Elastography - How To Do It? Ultrasound Int open. 2017 Sep;3(4):E137-E149.
10. Havre RF, Waage JR, Gilja OH, Odegaard S, Nesje LB. Real-Time Elastography: Strain Ratio Measurements Are Influenced by the Position of the Reference Area. Ultraschall Med. 2011 Jun 10.
11. Bamber J, Cosgrove D, Dietrich CF, Fromageau J, Bojunga J, Calliada F, *et al.* EFSUMB guidelines and recommendations on the clinical use of ultrasound elastography. Part 1: Basic principles and technology. Ultraschall Med. 2013 Apr;34(2):169-184.
12. Giovannini M, Thomas B, Erwan B, et al. Endoscopic ultrasound elastography for evaluation of lymph nodes and pancreatic masses: a multicenter study. World J Gastroenterol. 2009 Apr;15(13):1587-1593.
13. Iglesias-Garcia J, Larino-Noia J, Abdulkader I, Forteza J, Dominguez-Munoz JE. Quantitative endoscopic ultrasound elastography: an accurate method for the differentiation of solid pancreatic masses. Gastroenterology. 2010 Oct;139(4):1172-1180.
14. Cartana ET, Gheonea DI, Saftoiu A. Advances in endoscopic ultrasound imaging of colorectal diseases. World J Gastroenterol. 2016 Feb 7;22(5):1756-1766.
15. Li X, Xu W, Shi J, Lin Y, Zeng X. Endoscopic ultrasound elastography for differentiating between pancreatic adenocarcinoma and inflammatory masses: a meta-analysis. World J Gastroenterol. 2013 Oct 7;19(37):6284-6291.
16. Mei M, Ni J, Liu D, Jin P, Sun L. EUS elastography for diagnosis of solid pancreatic masses: a meta-analysis. Gastrointest Endosc. 2013 Apr;77(4):578-589.
17. Hu D-M, Gong T-T, Zhu Q. Endoscopic ultrasound elastography for differential diagnosis of pancreatic masses: a meta-analysis. Dig Dis Sci. 2013 Apr;58(4):1125-1131.
18. Dietrich CF, Cantisani V. Current status and perspectives of elastography. Eur J Radiol. 2014 Mar;83(3):403-404.
19. Iglesias-Garcia J, Larino-Noia J, Abdulkader I, Forteza J, Dominguez-Munoz JE. EUS elastography for the characterization of solid pancreatic masses. Gastrointest Endosc. 2009 Dec;70(6):1101-1108.
20. Iglesias-Garcia J, Lindkvist B, Lariño-Noia J, Domínguez-Muñoz JE. Endoscopic ultrasound elastography. Endosc ultrasound. 2012 Apr;1(1):8-16.
21. Mayerle J, Beyer G, Simon P, Dickson EJ, Carter RC, Duthie F, *et al.* Prospective cohort study comparing transient EUS guided elastography to EUS-FNA for the diagnosis of solid pancreatic mass lesions. Pancreatology. 2016 Jan-Feb;16(1):110-114.
22. Kongkam P, Lakananurak N, Navicharern P, Chantarojanasiri T, Aye K, Ridtitid W, *et al*. Combination of EUS-FNA and elastography (strain ratio) to exclude malignant solid pancreatic lesions: A prospective single-blinded study. J Gastroenterol Hepatol. 2015 Nov;30(11):1683-1689.
23. Rustemovic N, Opacic D, Ostojic Z, Opacic M, Ledinsky I, Višijić A, *et al.* Comparison of elastography methods in

patients with pancreatic masses. Endosc Ultrasound. 2014 Apr;3(Suppl 1):S4.
24. Havre RF, Odegaard S, Gilja OH, Nesje LB. Characterization of solid focal pancreatic lesions using endoscopic ultrasonography with real-time elastography. Scand J Gastroenterol. 2014;49(6):742-751.
25. Dawwas MF, Taha H, Leeds JS, Nayar MK, Oppong KW. Diagnostic accuracy of quantitative EUS elastography for discriminating malignant from benign solid pancreatic masses: a prospective, single-center study. Gastrointest Endosc. 2012 Nov;76(5):953-961.
26. Figueiredo FAF, da Silva PM, Monges G, Bories E, Pesenti C, Caillol F, *et al.* Yield of contrast-enhanced power doppler endoscopic ultrasonography and strain ratio obtained by eus-elastography in the diagnosis of focal pancreatic solid lesions. Endosc ultrasound. 2012 Oct;1(3):143-149.
27. Okasha HH, Mahdy RE, Elkholy S, Hassan MS, El-Mazny AN, Hadad KEE, *et al.* Endoscopic ultrasound (EUS) elastography and strain ratio, could it help in differentiating malignant from benign pancreatic lesions? Medicine (Baltimore). 2018 Sep;97(36):e11689.
28. Saftoiu A, Vilmann P, Gorunescu F, Gheonea DI, Gorunescu M, Ciurea T, *et al.* Neural network analysis of dynamic sequences of EUS elastography used for the differential diagnosis of chronic pancreatitis and pancreatic cancer. Gastrointest Endosc. 2008 Dec;68(6):1086-1094.
29. Saftoiu A, Vilmann P, Gorunescu F, Janssen J, Hocke M, Larsen M, *et al*. Accuracy of endoscopic ultrasound elastography used for differential diagnosis of focal pancreatic masses: a multicenter study. Endoscopy. 2011 Jul;43(7):596-603.
30. Cosgrove D, Piscaglia F, Bamber J, Bojunga J, Correas JM, Gilja OH, *et al*. EFSUMB guidelines and recommendations on the clinical use of ultrasound elastography. Part 2: Clinical applications. Ultraschall Med. 2013 Jun;34(3):238-253.
31. Cui X-W, Jenssen C, Saftoiu A, Ignee A, Dietrich CF. New ultrasound techniques for lymph node evaluation. World J Gastroenterol. 2013 Aug;19(30):4850-4860.
32. Janssen J, Dietrich CF, Will U, Greiner L. Endosonographic elastography in the diagnosis of mediastinal lymph nodes. Endoscopy. 2007 Nov;39(11):952-957..
33. Saftoiu A, Vilmann P, Hassan H, Gorunescu F. Analysis of endoscopic ultrasound elastography used for characterisation and differentiation of benign and malignant lymph nodes. Ultraschall Med. 2006 Dec;27(6):535-542.
34. Paterson S, Duthie F, Stanley AJ. Endoscopic ultrasound-guided elastography in the nodal staging of oesophageal cancer. World J Gastroenterol. 2012 Mar 7;18(9):889-895.
35. Xu W, Shi J, Zeng X, Li X, Xie WF, Guo J, *et al.* EUS elastography for the differentiation of benign and malignant lymph nodes: a meta-analysis. Gastrointest Endosc. 2011 Nov;74(5):1001-1004.
36. Saftoiu A, Vilmann P, Ciurea T, Popescu GL, Iordache A, Hassan H, *et al.* Dynamic analysis of EUS used for the differentiation of benign and malignant lymph nodes. Gastrointest Endosc. 2007 Aug;66(2):291-300.
37. Havre RF, Leh SM, Gilja OH, et al. Differentiation of Metastatic and Non-Metastatic Mesenteric Lymph Nodes by Strain Elastography in Surgical Specimens. Ultraschall Med. 2016 Aug;37(4):366-372.
38. Dietrich CF, Jenssen C, Herth FJF. Endobronchial ultrasound elastography. Endosc ultrasound. 2016 Jul-Aug;5(4):233-238.
39. Dietrich CF, Jenssen C, Arcidiacono PG, Cui XW, Giovannini M, Hocke M, et al. Endoscopic ultrasound: Elastographic lymph node evaluation. Endosc ultrasound. 2015 Jul-Sep;4(3):176-190.
40. Cui XW, Hocke M, Jenssen C, Ignee A, Klein S, Schreiber-Dietrich D, et al. Conventional ultrasound for lymph node evaluation, update 2013. Z Gastroenterol. 2014 Feb; 52(2):212-221.
41. Jenssen C, Dietrich CF. Endoscopic ultrasound-guided fine-needle aspiration biopsy and trucut biopsy in gastroenterology - An overview. Best Pract Res Clin Gastroenterol. 2009;23(5):743-759.
42. Valero M, Robles-Medranda C. Endoscopic ultrasound in oncology: An update of clinical applications in the gastrointestinal tract. World J Gastrointest Endosc. 2017 Jun;9(6):243-254.
43. Dietrich CF, Jenssen C, Hocke M, Cui X-W, Woenckhaus M, Ignee A. Imaging of gastrointestinal stromal tumours with modern ultrasound techniques - a pictorial essay. Z Gastroenterol. 2012 May;50(5):457-467.
44. Kocaman O, Senturk H, Danalioglu A, Türkdoğan K, Arabacı E, Yıldız K, *et al.* Endosonography and elastography in the diagnosis of esophageal tuberculosis. Turk J Gastroenterol. 2013;24(3):290-291.
45. Dietrich CF, Saftoiu A, Jenssen C. Real time elastography endoscopic ultrasound (RTE-EUS), a comprehensive review. Eur J Radiol. 2014 Mar;83(3):405-414.
46. Waage JER, Leh S, Rosler C, Pfeffer F, Bach SP, Havre RF, et al. Endorectal ultrasonography, strain elastography and MRI differentiation of rectal adenomas and adenocarcinomas. Colorectal Dis. 2015 Feb;17(2):124-131.
47. Waage JER, Havre RF, Odegaard S, Leh S, Eide GE, Baatrup G. Endorectal elastography in the evaluation of rectal tumours. Colorectal Dis. 2011 Oct;13(10):1130-1137.

48. Coban S, Basar O, Brugge WR. Future Directions for Endoscopic Ultrasound: Where Are We Heading? Gastrointest Endosc Clin N Am. 2017 Oct;27(4):759-772.
49. Zhang L, Sanagapalli S, Stoita A. Challenges in diagnosis of pancreatic cancer. World J Gastroenterol. 2018;24(19):2047-2060.
50. Sidhu PS, Cantisani V, Dietrich CF, Gilja OH, Saftoiu A, Bartels E, *et al.* The EFSUMB Guidelines and Recommendations for the Clinical Practice of Contrast-Enhanced Ultrasound (CEUS) in Non-Hepatic Applications: Update 2017 (Long Version). Ultraschall Med. 2018 Apr;39(2):e2-e44.
51. Fusaroli P, Serrani M, De Giorgio R, D'Ercole MC, Ceroni L, Lisotti A, *et al.*Contrast Harmonic-Endoscopic Ultrasound Is Useful to Identify Neoplastic Features of Pancreatic Cysts (With Videos). Pancreas. 2016 Feb;45(2):265-268.
52. Ran L, Zhao W, Zhao Y, Bu H. Value of contrast-enhanced ultrasound in differential diagnosis of solid lesions of pancreas (SLP): A systematic review and a meta-analysis. Medicine (Baltimore). 2017 Jul;96(28):e7463.
53. He X-K, Ding Y, Sun L-M. Contrast-enhanced endoscopic ultrasound for differential diagnosis of pancreatic cancer: an updated meta-analysis. Oncotarget. 2017 Jul;8(39):66392-66401.
54. Lee TY, Cheon YK, Shim CS. Clinical role of contrast-enhanced harmonic endoscopic ultrasound in differentiating solid lesions of the pancreas: a single-center experience in Korea. Gut Liver. 2013 Sep;7(5):599-604.
55. Choi J-H, Seo DW. The Expanding Role of Contrast-Enhanced Endoscopic Ultrasound in Pancreatobiliary Disease. Gut Liver. 2015 Nov 23;9(6):707-13.
56. Matsubara H, Itoh A, Kawashima H, *et al*. Dynamic quantitative evaluation of contrast-enhanced endoscopic ultrasonography in the diagnosis of pancreatic diseases. Pancreas. 2011 Oct;40(7):1073-1079.
57. Gincul R, Palazzo M, Pujol B, Tubach F, Palazzo L, Lefort C, et al. Contrast-harmonic endoscopic ultrasound for the diagnosis of pancreatic adenocarcinoma: a prospective multicenter trial. Endoscopy. 2014 May;46(5):373-379.
58. Saftoiu A, Vilmann P, Bhutani MS. The role of contrast-enhanced endoscopic ultrasound in pancreatic adenocarcinoma. Endosc ultrasound. 2016 Nov-Dec;5(6):368-372.
59. Gong T, Hu D, Zhu Q. Contrast-enhanced EUS for differential diagnosis of pancreatic mass lesions: a meta-analysis. Gastrointest Endosc. 2012 Aug;76(2):301-309.
60. D'Onofrio M, Biagioli E, Gerardi C, Canestrini S, Rulli E, Crosara S, *et al*. Diagnostic performance of contrast-enhanced ultrasound (CEUS) and contrast-enhanced endoscopic ultrasound (ECEUS) for the differentiation of pancreatic lesions: a systematic review and meta-analysis. Ultraschall Med. 2014 Dec;35(6):515-521.
61. Fusaroli P, Spada A, Mancino MG, Caletti G. Contrast harmonic echo-endoscopic ultrasound improves accuracy in diagnosis of solid pancreatic masses. Clin Gastroenterol Hepatol. 2010 Jul;8(7):629-34.
62. Gheonea DI, Streba CT, Ciurea T, Saftoiu A. Quantitative low mechanical index contrast-enhanced endoscopic ultrasound for the differential diagnosis of chronic pseudotumoral pancreatitis and pancreatic cancer. BMC Gastroenterol. 2013 Jan;13:2.
63. Dietrich CF, Dong Y, Froehlich E, Hocke M. Dynamic contrast-enhanced endoscopic ultrasound: A quantification method. Endosc ultrasound. 2017 Jan-Feb;6(1):12-20.
64. Sugimoto M, Takagi T, Hikichi T, Suzuki R, Watanabe K, Nakamura J, *et al*. Conventional versus contrast-enhanced harmonic endoscopic ultrasonography-guided fine-needle aspiration for diagnosis of solid pancreatic lesions: A prospective randomized trial. Pancreatology. 2015 Sep-Oct;15(5):538-541.
65. Imazu H, Uchiyama Y, Matsunaga K, Ikeda K, Kakutani H, Sasaki Y, *et al*. Contrast-enhanced harmonic EUS with novel ultrasonographic contrast (Sonazoid) in the preoperative T-staging for pancreaticobiliary malignancies. Scand J Gastroenterol. 2010 Jun;45(6):732-738.
66. Seicean A, Badea R, Stan-Iuga R, Mocan T, Gulei I, Pascu O. Quantitative contrast-enhanced harmonic endoscopic ultrasonography for the discrimination of solid pancreatic masses. Ultraschall Med. 2010 Dec;31(6):571-576.
67. Iglesias-Garcia J, Lindkvist B, Lariño-Noia J, Abdulkader-Nallib I, Dominguez-Muñoz JE. Differential diagnosis of solid pancreatic masses: contrast-enhanced harmonic (CEH-EUS), quantitative-elastography (QE-EUS), or both? United Eur Gastroenterol J. 2017 Mar;5(2):236-246.
68. Kamata K, Kitano M, Omoto S, Kadosaka K, Miyata T, Yamao K, *et al*. Contrast-enhanced harmonic endoscopic ultrasonography for differential diagnosis of pancreatic cysts. Endoscopy. 2016 Jan;48(1):35-41.
69. Serrani M, Lisotti A, Caletti G, Fusaroli P. Role of contrast harmonic-endoscopic ultrasound in pancreatic cystic lesions. Endosc ultrasound. 2017 Jan-Feb;6(1):25-30.
70. Yamao K, Nakamura T, Suzuki T, Sawaki A, Hara K, Kato T, *et al*. Endoscopic diagnosis and staging of mucinous cystic neoplasms and intraductal papillary-mucinous tumors. J Hepatobiliary Pancreat Surg. 2003;10(2):142-146.
71. Kitano M, Sakamoto H, Matsui U, Ito Y, Maekawa K, von Schrenck T, *et al*. A novel perfusion imaging technique

of the pancreas: contrast-enhanced harmonic EUS (with video). Gastrointest Endosc. 2008 Jan;67(1):141-150.
72. European Study Group on Cystic Tumours of the Pancreas. European evidence-based guidelines on pancreatic cystic neoplasms. Gut. 2018 May;67(5):789-804.
73. Fusaroli P, Kypraios D, Mancino MG, Spada A, Benini MC, Bianchi M, *et al*. Interobserver agreement in contrast harmonic endoscopic ultrasound. J Gastroenterol Hepatol. 2012 Jun;27(6):1063-1069.
74. Hocke M, Ignee A, Dietrich C. Role of contrast-enhanced endoscopic ultrasound in lymph nodes. Endosc ultrasound. 2017 Jan;6(1):4-11.
75. Poanta L, Serban O, Pascu I, Pop S, Cosgarea M, Fodor D. The place of CEUS in distinguishing benign from malignant cervical lymph nodes: a prospective study. Med Ultrason. 2014 Mar;16(1):7-14.
76. Aoki T, Moriyasu F, Yamamoto K, Shimizu M, Yamada M, Imai Y. Image of tumor metastasis and inflammatory lymph node enlargement by contrast-enhanced ultrasonography. World J Radiol. 2011 Dec;3(12):298-305.
77. Ignee A, Jenssen C, Hocke M, Dong Y, Wang WP, Cui XW, *et al*. Contrast-enhanced (endoscopic) ultrasound and endoscopic ultrasound elastography in gastrointestinal stromal tumors. Endosc ultrasound. 2017 Jan-Feb;6(1):55-60.
78. Kannengiesser K, Mahlke R, Petersen F, Peters A, Ross M, Kucharzik T, *et al*. Contrast-enhanced harmonic endoscopic ultrasound is able to discriminate benign submucosal lesions from gastrointestinal stromal tumors. Scand J Gastroenterol. 2012 Dec;47(12):1515-1520.
79. Tozer GM. Measuring tumour vascular response to antivascular and antiangiogenic drugs. Br J Radiol. 2003;76 Spec No 1:S23-35.
80. Matsui S, Kudo M, Kitano M, Asakuma Y. Evaluation of the Response to Chemotherapy in Advanced Gastric Cancer by Contrast-Enhanced Harmonic EUS. Hepatogastroenterology. 2015 May;62(139):595-598.
81. Wang Y, Li L, Wang Y-XJ, Cui NY, Zou SM, Zhou CW, *et al*. Time-intensity curve parameters in rectal cancer measured using endorectal ultrasonography with sterile coupling gels filling the rectum: correlations with tumor angiogenesis and clinicopathological features. Biomed Res Int. 2014;2014:587806.
82. Tranquart F, Mercier L, Frinking P, Gaud E, Arditi M. Perfusion quantification in contrast-enhanced ultrasound (CEUS)--ready for research projects and routine clinical use. Ultraschall Med. 2012 Jul;33 Suppl 1:S31-8.
83. Cartana E-T, Gheonea DI, Cherciu IF, Streața I, Uscatu CD, Nicoli ER, *et al*. Assessing tumor angiogenesis in colorectal cancer by quantitative contrast-enhanced endoscopic ultrasound and molecular and immunohistochemical analysis. Endosc ultrasound. 2018 May-Jun;7(3):175-183.
84. Park DH, Choi J-H, Oh D, Lee SS, Seo DW, Lee SK, *et al*. Endoscopic ultrasonography-guided ethanol ablation for small pancreatic neuroendocrine tumors: results of a pilot study. Clin Endosc. 2015 Mar;48(2):158-164.
85. Giday SA, Magno P, Gabrielson KL, Buscaglia JM, Canto MI, Ko CW, *et al*. The utility of contrast-enhanced endoscopic ultrasound in monitoring ethanol-induced pancreatic tissue ablation: a pilot study in a porcine model. Endoscopy. 2007 Jun;39(6):525-529.

GRUPUGE Recommendations

ENDOSCOPIC ULTRASOUND IN ONCOLOGY

2019