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Endoscopic ultrasound in oncology: An update of clinical applications in the gastrointestinal tract

Manuel Valero, Carlos Robles-Medranda

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Abstract

An accurate staging is necessary to select the best treatment and evaluate prognosis in oncology. Staging usually begins with noninvasive imaging such as

computed tomography, magnetic resonance imaging or positron emission tomography. In the absence of distant metastases, endoscopic ultrasound plays an important role in the diagnosis and staging of gastrointestinal tumors, being the most accurate modality for local-regional staging. Its use for tumor and nodal involvement in pre-surgical evaluation has proven to reduce unnecessary surgeries. The aim of this article is to review the current role of endoscopic ultrasound in the diagnosis and staging of esophageal, gastric and colorectal cancer.

Key words: Endoscopic ultrasound; Staging; Esophageal cancer; Gastrointestinal cancer; Gastric cancer; Colorectal cancer

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Core tip: Endoscopic ultrasound (EUS) has an important role in staging, establishing prognosis and optimizing therapeutic decisions. Also, it has proved to be a useful alternative therapeutic modality in surgery. In terms of cost-benefit, it reduces the number of unnecessary diagnostic or therapeutic procedures, leading to lower morbidity and mortality rates and reduced cost in cancer treatment. This review summarizes the current role of EUS in the diagnosis and staging of esophageal, gastric and colorectal cancer.

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INTRODUCTION

Endoscopic ultrasound (EUS) was first used in 1980

as a technology prototype for pancreatic cancer evaluation^[1]. It was designed as a combination of two techniques, endoscopy and ultrasound, allowing the visualization of the gastrointestinal mucosa as well as the tract wall in deep and surrounding structures. In 1989 its standardized indications in clinical practice were described^[2]. Due to the constant evolution of this technology, it is now considered an important diagnostic and therapeutic method in the oncology field. EUS has an important role in staging, establishing prognosis and optimizing therapeutic decisions^[3]. Also, it has proved to be a useful alternative therapeutic modality in surgery. In terms of cost-benefit, it reduces the number of unnecessary diagnostic or therapeutic procedures, leading to lower morbidity and mortality rates and reduced cost in cancer treatment^[4,5]. The TNM classification (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). Staging usually begins using noninvasive imaging techniques such as computed tomography (CT), magnetic resonance imaging (MRI), or positron emission tomography (PET), which are generally better than EUS for excluding M. In the absence of metastasis, EUS has proved to be an accurate modality for assessing T and N^[2]. Moreover, the development of EUS-related technology such as fine needle aspiration (FNA), high frequency catheter probe, elastography and contrast enhancement has helped to improve EUS staging accuracy. EUS indications in oncology is therefore increasing^[6]. The aim of this review is to summarize the current role of EUS in the staging of esophageal, gastric and colorectal cancer.

ESOPHAGEAL CANCER

Characteristics of esophageal cancer and clinical implications

The prognosis of esophageal cancer (EC) is poor because these tumors are usually detected in an advanced stage. Surgery is not possible in most cases and has a high rate of morbidity and mortality. The level of tumor invasion and lymph node metastasis will determine treatment and prognosis. Therefore, EUS plays a vital role by providing an accurate T and N staging, which allows deciding on the best treatment^[7]. The use of EUS evaluation in preoperative staging has led to a mortality reduction of 42.1% and a better recurrence-free survival rate, compared to patients with no EUS evaluation^[8]. According to the TNM classification (Table 1), superficial EC includes mucosal and submucosal involvement (Tis, T1a or T1b)^[9]. Patients with any nodal involvement (N⁺) or advance tumors (T2-T4a) (Figure 1) need preoperative neoadjuvant chemoradiotherapy, whereas T1 patients with no nodal metastasis can benefit from endoscopic (Tis, T1a N0) or surgical resection (T1bN0)^[10-12]. When different staging methods were compared, CT, MRI and PET-scan showed themselves

to be better than EUS in evaluating distant metastasis (M), however EUS proved superiority in the detection of tumor stage (T) and lymph nodes (N)^[13-16]. One method does not have to exclude the other. The incorporation of CT, PET and EUS in preoperative staging reduces the number of unnecessary surgical procedures from 44% to 21%^[17].

The role of EUS in T staging

EC limited to the mucosa (Tis, T1a) can be treated effectively with minimally invasive endoscopic therapy, whereas submucosal (T1b) EC carries relatively high risk of lymph node metastasis and requires surgical resection. According to a meta-analysis by Puli *et al.*^[18] (49 articles), 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. The accuracy was higher for T3-T4 lesions (> 90%) than T1-T2 (65%). However, a study by Thosani *et al.*^[19] reported, on the analysis of 1019 patients with only superficial EC, that EUS sensitivity and specificity was 85% and 87% for T1a and 86% and 86% for T1b respectively, with an overall EUS accuracy for superficial EC staging of > 93%.

The role of EUS in N staging

The lymph node (LN) metastasis in EC is considered the main fact that influences prognosis and it depends on the number of nodes involved. This pathology has a high rate of LN involvement at an early stage. T1sm (T1b) disease has a 15% to 30% rate of LN dissemination. The 7th edition of the AJCC (Table 1) classifies the N stage according to the number of metastasized lymph nodes in N1 (1 to 2), N2 (3 to 6), and N3 (≥ 7). The use of EUS evaluation in preoperative staging has led to a mortality reduction of 42.1% and a better recurrence-free survival rate, compared to patients with no EUS evaluation^[8]. According to the TNM classification (Table 1)^[9], the presence of node metastasis indicates the need of neoadjuvant therapy. Therefore, identification of the N stage is mandatory. PET and CT have a low accuracy (51%) compared to EUS^[20]. The evaluation of the LN features using EUS have shown that malignant nodes tend to be larger than 1 cm, round, sharply demarcated, and hypoechoic. When all these features are present there is an 85% chance of malignancy. However, only 25% of malignant LN have all four features^[21]. A systematic review found that EUS has a sensitivity range of 59.5% to 100% and a specificity range of 40% to 100% for N staging^[22]. Puli *et al.*^[18] described a EUS sensitivity for N stage of 85% and showed that the use of FNA substantially improves 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%. Chen *et al.*^[23] found an accuracy rate of 99.4% using EUS-FNA. In patients with EC, the identification of a celiac lymph node is synonymous to LN metastasis in 90% of the cases regardless of echo features and size and

Table 1 TNM in esophageal cancer

Primary tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	High-grade dysplasia
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 invades adventitia
T4	Tumor invades adjacent structures
T4a	Resectable tumor invading pleura, pericardium, or diaphragm
T4b	Unresectable tumor invading other adjacent structures, such as the aorta, vertebral body, and trachea
Regional lymph nodes (N)	
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 7 or more regional lymph nodes
Distant metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis

therefore indicates a poor prognosis^[24]. EUS-FNA for celiac lymph node diagnosis has shown a sensitivity of 72% to 83%, a specificity of 85% to 98%, and an accuracy of 94%^[25].

Limitations

The role of EUS has some limitations. It may be less accurate for assessing the T1-T2 stage compared with T3-T4. According to some authors there is a trend to overstaging the depth of the submucosal invasion, with a low accuracy rate in early T staging (64%)^[26]. The use of high frequency catheter probes may improve the diagnostic accuracy in early lesions from 83% to 92%, but the results are heterogeneous^[27,28]. EUS criteria are not accurate after neoadjuvant radio-chemotherapy because EUS poorly differentiates tumor from necrosis or inflammatory reaction^[29]. The presence of esophageal malignant stenosis that cannot be overcome can make TNM evaluation more difficult. A recent multi-center study suggested that routine EUS examinations may not be required in all patients with EC as the inability to advance a diagnostic gastroscope through a malignant stricture correlates 100% with locally advanced disease, so that performing a EUS does not change the treatment decision^[30].

Role of EUS in Barrett's esophagus

EUS has long been used to evaluate Barrett's esophagus (BE)^[6]. In the case of BE associated with high-grade dysplasia (HGD) or early (T1m) esophageal adenocarcinoma (EAC), the patient may benefit from endoscopic resection, but if EUS shows an advanced disease with tumor invading the submucosal, or beyond, or lymph node involvement, endoscopic therapy may

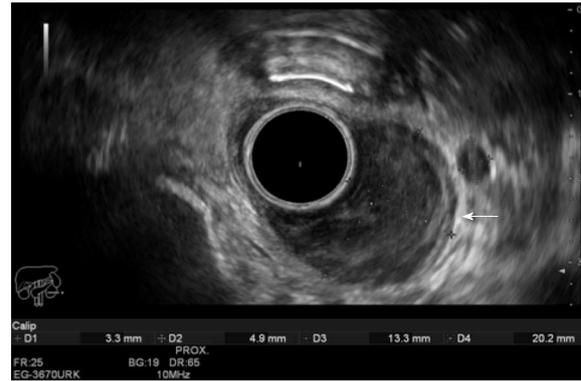


Figure 1 Esophageal carcinoma staging by endoscopic ultrasound T2 N1. The tumor is being measure (13.3 mm × 20.2 mm). It invades up to the muscularis propria (white arrow). A round, sharply demarcated and hypoechoic lymph node can be seen next to the tumor. EUS images were obtained using a Hitachi-Avius console with a radial scope EG-3630URK (from Pentax Medical). EUS: Endoscopic ultrasound.

not be warranted. Qumseya *et al*^[31] showed in a recent meta-analysis that 14% of patients referred to EUS for BE associated with HGD or EAC will have advanced cancer (> T1sm or > N1) detected by EUS that is not amenable to endoscopic treatment and which therefore changes the therapeutic approach. With EUS it was found that 4% of these patients have advanced disease in the absence of nodules. The sensitivity and specificity for T stage was 56% and 89% and for N stage was 71% and 94 % respectively^[31]. However, even the data mentioned, the American College of Gastroenterology has stated that EUS routine staging of patients with BE before EMR is unwarranted as clinical decision making will rest with the EMR findings and given the possibility of over- and under-staging in patients with superficial EAC^[32-35]. In case of T1a lesions the rate of lymph node (LN) involvement is low, making these lesions optimally treated by EMR^[36,37]. In patients with known T1b sm1 disease, there is conflicting data with respect to the likelihood of LN invasion^[38,39]. The evidence of LN involvement, especially if substantiated by FNA, means that any attempt at endoscopic therapy would be palliative and therefore EUS may have a role in assessing and sampling regional LN, given the increased prevalence of lymph node involvement in these patients compared with less advanced disease^[19].

GASTRIC CANCER

Characteristics of gastric cancer and clinical implications

Gastric cancer (GC) is the fourth most common cancer and the second cause of cancer-related deaths (10%)^[40]. An accurate staging (Table 2) can be extremely useful in providing patients with the best therapeutic option. Patients with early gastric cancer, in the presence of favorable prognosis features (well-differentiated carcinoma, limited to the mucosa, diameter < 2 cm, absence of ulceration) and no lymph node involvement

Table 2 TNM in gastric cancer

Primary tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma <i>in situ</i> : 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
Regional lymph nodes (N)	
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
Distant metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis

(N0) can benefit from endoscopic resection rather than surgical resection^[41,42]. On the other hand, patients with advanced gastric cancer (T3-T4 tumors or N⁺) need to be treated with neoadjuvant therapy (chemotherapy, radiotherapy or both)^[43,44].

CT is a frequent imaging method for the preoperative staging of GC^[45]. It has a high accuracy for distant metastasis (M), however its overall accuracy for loco-regional staging (T and N stages) is low, ranging from 65% to 85%^[46,47]. The CT sensitivity and specificity for N stage is 77% and 78%, respectively^[48]. No better results appear to be achievable with MRI or PET^[48-50].

Thus, these imaging devices are mostly used to diagnose locally advanced lesions (T3-T4 or N⁺) or distant metastasis than early stages of GC. On the contrary, EUS is an accurate device for the loco-regional staging^[51,52] (Figure 2). The employment of EUS in the preoperative stage of GC has shown to change the therapeutic management in 30% of cases, resulting in more limited surgical resections, especially in stages T1 and T3^[53].

The role of EUS in T staging

A recent meta-analysis by Mocellin *et al.*^[54] and the Cochrane Collaboration Group (2015) evaluated 66 articles ($n = 7747$) about GC staged with EUS. The aim was to evaluate EUS ability to separate patients with GC who would best benefit from surgery without preoperative radio-chemotherapy (T1-T2) from those with advanced tumors (T3-T4) who are likely to benefit from neoadjuvant therapy. They found EUS sensitivity and specificity to discriminate T1-T2 from T3-T4 lesions to be 86% and 90% respectively. A second analysis



Figure 2 Gastric adenocarcinoma staging by endoscopic ultrasound T3 N0. The tumor overcomes the muscularis propria (blue arrow) and penetrates the subserosal connective tissue (white arrow). EUS images were obtained using a Hitachi-Avius console with a radial scope EG-3630URK (from Pentax Medical). EUS: Endoscopic ultrasound.

was made to evaluate EUS ability to discriminate between patients with superficial cancers (T1 from T2 and T1a from T1b), with the intention of identifying patients who would benefit from endoscopic resection rather than surgery. The sensitivity and specificity of EUS to distinguish T1 (early GC) from T2 (muscle-infiltrating) was 85% and 90% respectively. As for the capacity of EUS to distinguish between T1a (mucosal) vs T1b (submucosal), they showed that the sensitivity and specificity was 87% and 75% respectively. They concluded that EUS can distinguish between superficial (T1-T2) and advanced (T3-T4) primary tumors with a sensitivity and specificity greater than 85%. This performance is maintained for the discrimination between T1 and T2 superficial tumors. However, EUS diagnostic accuracy is lower when it comes to distinguishing between the different types of early tumors (T1a vs T1b)^[54]. This conclusion correlates with Mocellin *et al.*^[55] previous results (2011) when they described that EUS can differentiate T1-2 from T3-4 GC with high accuracy (sensitivity of 86% and specificity of 91%). Cardoso *et al.*^[56] (2012) also showed that EUS seems to identify advanced T stage (T3 and T4) better than it identifies less advanced T stage or N stage, with a combined accuracy for T staging of 75%. Puli *et al.*^[57] (2008) evaluated 22 studies ($n = 1896$) and described the usefulness of EUS in GC. The sensitivity and specificity by stage were, 88.1% and 100% for T1, 82.3% and 95.6% for T2, 89.7% and 94.7% for T3, and 99.2% and 96.7% for T4. Incidentally, EUS for T stage detection was more accurate in advanced cancer than in early cancer. Kwee *et al.*^[58] (2008) showed in a systematic review (18 studies), the accuracy of EUS in differentiating mucosal (T1m) from deeper GC (> T1sm) and found that sensitivity and specificity of EUS in detecting cancerous extension beyond the mucosa ranged from 18.2% to 100% (median 87.8%) and from 34.7% to 100% (median 80.2%) respectively. They concluded that the studies showed too much heterogeneity and it is still unclear whether EUS can

Table 3 TNM in rectal cancer

Primary tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma <i>in situ</i> : Intraepithelial or invasion of lamina propria
T1	Tumor invades submucosa
T2	Tumor invades muscularis propria
T3	Tumor invades through the muscularis propria into pericorectal tissues
T4a	Tumor penetrates to the surface of the visceral peritoneum
T4b	Tumor directly invades or is adherent to other organs or structures
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 node
N1b	Metastasis in 2-3 regional lymph nodes
N1c	Tumor deposit(s) in the subserosa, mesentery, or non-peritonealized pericolic or perirectal tissues without regional nodal 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)	
M0	No distant metastasis
M1	Distant metastasis
M1a	Metastasis confined to one organ or site (for example, liver, lung, ovary, nonregional node)
M1b	Metastases in more than one organ/site or the peritoneum

accurately differentiate between mucosal and deeper GC^[58].

The role of EUS in N staging

The accuracy of EUS for N staging has shown remarkable heterogeneity of results. Mocellin *et al*^[54] described after the evaluation of 44 studies ($n = 3573$) an overall sensitivity and specificity of 83% and 67% respectively^[54]. Cardoso *et al*^[56] reported accuracy for N stage of 64%, sensitivity of 74%, and specificity of 80%. These results were due to the low possibility of detecting metastasized lymph nodes that are distant from the lesion^[56]. Kwee *et al*^[59] found that sensitivity and specificity of EUS varied from 16.7% to 95.3% (median 70.8%) and 48.4% to 100% (median, 84.6%). Puli *et al*^[57] after the analysis of 22 studies ($n = 1896$) reported a sensitivity for N1 of 58.2% and N2 of 64.9%. The pooled sensitivity to diagnose distant metastasis was 73.2%.

Limitations

There is a remarkable heterogeneity of the evidence currently available about the ability of EUS to differentiate T1a vs T1b tumors and to diagnose lymph node metastasis (N0 vs N+). Therefore, physicians should be cautious at the time of interpreting these results. Tumor features like size and location may affect diagnostic performance of EUS. A tumor size greater than 3 cm is associated with overstaging by EUS and decreases the diagnostic accuracy to 50%^[60]. The cardia, the greater

curve of upper body, the lesser curve at the incisura and the pyloric channel are the most challenging areas to examine^[61].

Gastric lymphoma

Even though CT has proved useful for evaluating an abnormal gastric wall thickening, EUS, on the other hand, has shown itself to be superior for examining nodal involvement, extension and depth of tumor invasion^[62]. The EUS diagnostic accuracy in gastric lymphoma is 91%-95% for T stage and 77%-83% for N stage^[63,64]. The use of EUS-FNA combined with flow cytometry and immunohistochemistry can improve N staging accuracy substantially^[65].

EUS has also shown a significant impact on treatment decisions. Gastric lymphoma confined to the mucosal and submucosal (T1) can simply be treated with *H. pylori* eradication therapy. However, if EUS shows deeper invasion, chemotherapy, radiation or surgical treatment may be necessary^[66]. Moreover, EUS has proven to be useful for surveillance of recurrences at an early stage^[62].

RECTAL, COLON AND ANAL CANCER

Characteristics of rectal cancer and clinical implications

Accurate staging in rectal cancer (RC) is crucial for choosing the best multimodal therapy. Treatment decisions and prognosis depends on both T and N stage of the disease at the time of diagnosis^[67]. In the absence of distant metastasis (M), EUS is the most accurate imaging modality for loco-regional staging (T and N stages) of rectal tumors^[68]. Stage I disease includes early rectal lesions (T1-T2 N0 M0) (Table 3). While T1 lesions can benefit from endoscopic mucosal resection or transanal endoscopic microsurgery, T2 lesions need surgery^[69,70]. Stage II disease with locally advanced cancer (T3-T4 N0 M0), or stage III with lymph node metastasis (T1-4 N1-2 M0) will benefit maximally and improve recurrence-free survival when neoadjuvant radio-chemotherapy is given^[71-74]. Preoperative biopsies of rectal tumors may fail to diagnose an invasive carcinoma, with up to 24% false negative results. The preoperative use of EUS reduces the rate of missed carcinomas from 21% to 3%^[75]. EUS compared to other imaging modalities (CT, PET/CT, MRI) is superior and more accurate in determining T stage (EUS: 87%, CT: 76% and MRI: 77%)^[70,76-77]. In N stage situations, it is also superior, but the difference is less obvious and accuracy varies between studies (EUS 63%-85%, CT 56%-79% and MRI 57%-85%)^[78-82]. Usually CT and PET/CT are used for distant metastasis diagnosis^[82]. It is also reported that when CT was the original mode of investigation but a further EUS was done, in 31% of the cases the mode of treatment was changed because of the result^[70]. The combination of CT and EUS seems to be the most cost-effective diagnostic strategy^[83]. MRI has less accuracy in the T stage than EUS does,

but provides a good definition of the circumferential resection margin (CRM). While EUS is more useful for staging early RC, MRI is indicated for staging advanced disease and defines CRM. Also, it can be used in the case of stenotic tumors, when EUS is less accurate. Thus, EUS and MRI are complementary and should be both used for preoperative staging^[81,84].

RC recurrence rates range from 20% to 50%, depending on how advanced the cancer is and if neoadjuvant therapy has been administered before surgery^[85,86]. It has been proven that there is a significant reduction in tumor recurrence when patients undergo EUS staging compared to those who do not^[87]. In addition to this, EUS can be used to evaluate the colorectal anastomosis during follow-up of patients operated for RC and confirm or rule out recurrence with 97% sensitivity, 100% specificity, 100% positive predictive value (PPV), 94% negative predictive value (NPV), and an overall accuracy of 98%^[88,89]. One limitation that has been attributed to EUS is its difficulty in differentiating between post-operative benign lesions and recurring cancer in post-operative lesions. However, the use of EUS-guided FNA increases the specificity from 57% to 97%^[85,86]. Thus, EUS has a key role in both preoperative staging and follow-up after surgery.

The role of EUS in T staging

Over- or under-staging leads to changes in a patient's treatment. Surgery instead of endoscopic resection and the use of chemoradiotherapy could be wrongly indicated when there is over-staging. On the other hand, under-staging with the lack of neoadjuvant indication could lead to an insufficient treatment. According to a recent review performed by Marone *et al.*^[90] (33 articles, $n = 4976$), EUS assesses the tumor penetration depth into the rectal wall with an overall accuracy for T stage of about 84%, ranging from 63% to 96%, while the reported accuracy of CT and MRI are 65%-75% and 75%-85%, respectively. They showed also that EUS accuracy for T stage is strictly related to the depth of infiltration, being lower for T2 stage than for early (T1) or advanced (T3-4) RC (T1: 88%, T2: 78.4%, T3: 85.4% and T4: 80.2%)^[90]. Similarly, a meta-analysis (42 studies, $n = 5039$ patients) showed that EUS has an overall RC staging sensitivity of 81%-96% and specificity of 91%-98%, showing higher sensitivity for advanced RC (95%) than early cancer (88%). The pooled sensitivity and specificity by stage was for T1: 88% and 98%, T2: 81% and 96%, T3: 96% and 91% and T4: 95% and 98%, respectively. The authors concluded that EUS should be the imaging method of choice for the T staging of RC^[91] (Figure 3). Superficial RC limited to the mucosa can be resected endoscopically. EUS has a high accuracy rate in differentiating T1 from T2 lesions, ranging from 81% to 95%, with an overstaging or understaging rate of 9%^[92]. Puli *et al.*^[93] evaluated, in a meta-analysis (11 studies, $n = 1791$), the efficacy of preoperative EUS in staging patients with RC confined to the mucosa (T0) and found that sensitivity was 97% and specificity 96%.

They concluded that EUS should be strongly considered for staging of early RCs^[93].

The role of EUS in N staging

EUS role in the determination of lymph node (LN) metastasis is less precise than T staging, with a mean accuracy of 74% (range 63%-85%)^[90]. However, the accuracy is still better than others imaging modalities like CT (56%-79%) or MRI (57%-85%)^[78-82]. Similarly, a meta-analysis including 35 articles showed that EUS has a sensitivity of 73% and specificity of 76% for N staging. This low EUS performance is related to the difficulty in evaluating distant metastatic LN that are out of EUS scanning, discriminating between inflammatory and metastatic LN and the tendency to overlook small metastatic LN compared to larger LN^[94-98]. The presence of all malignant features (enlarged node ≥ 1 cm, hypoechoic appearance, round shape, and smooth border) is related to 100% of PPV for malignancy, however this situation is seen in less than 25% of cases^[21]. It is known that there is a correlation between T stage and risk of LN involvement in patients with RC. The risk varies from 6%-11% for T1, 10%-35% for T2 and 26%-65% for T3-T4 RC^[99]. Similarly, the EUS accuracy for N staging also depends on T staging and seems to be better for advanced disease (84% in T3 compared to 48% in T1). This is explained by the fact that in T1 lesions metastatic nodes are possibly small^[98]. On the other hand, beside EUS limitations in N staging, EUS guided FNA can be used to balance and improve the accuracy from 75% to 87%^[100]. EUS-FNA has a sensitivity, specificity, PPV and NPV of 89%, 79%, 89% and 79% respectively^[97,101]. The fact that EUS-FNA has a moderate NPV (77%) for N staging means that LN metastases cannot be ruled out by a negative FNA^[102]. Even though most perirectal nodes detected by EUS in patients with RC are metastatic, it is important to confirm this. EUS-FNA should be indicated when results change the therapeutic strategy. The presence or absence of LN metastasis in T1-T2 lesions change the stage of the patient from I to III and indicates the chemoradiotherapy strategy. EUS-FNA changes patient management in 19% of the cases^[70,103].

Limitations

EUS performance is operator-dependent and accuracy improves with experience. This fact explains the wide range of overall accuracy for T and N staging between studies (63% to 95%)^[104,105]. A high inter-observer variability (61%-77%) has been described according to the experience of the operator, with overstaging values of 19% and understaging of 12%^[104]. Also, EUS seems to be less accurate in restaging RC after neoadjuvant therapy (NAT), due to the limitations in differentiating inflammation, edema, necrosis and fibrosis from neoplastic infiltration, with the risk of overstaging and overtreatment^[68,106,107]. EUS correctly predicts complete response to chemoradiation in 50%-63% of the cases. It has an overall accuracy for T stage of 48%, with 38%



Figure 3 Rectal adenocarcinoma staging by endoscopic ultrasound T4 N0. The tumor invasion overcomes the rectal wall and penetrates the prostate. There is a lack of separation plane between the tumor and the prostate (white arrow).



Figure 5 The same lesion presented in Figure 3 being evaluated by contrast enhanced ultrasonography. The white arrow shows the lymph node with no enhancement after the contrast application, which suggests malignancy. The endoscopic ultrasound-contrast enhancement was done using a Hitachi-Avius console with a radial scope EG-3630URK (from Pentax Medical) and a Sonovue contrast agent (from Bracco).

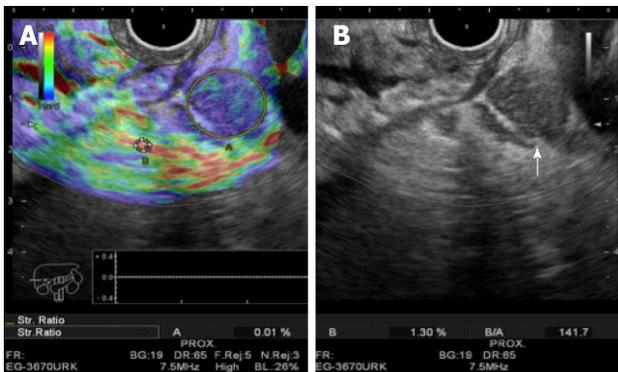


Figure 4 A lymph node being evaluated by elastography, for a gastric tumor staging. A: Qualitative elastography (color tones red-green-blue) shows the lesion with a blue-predominant color tone, which represents a hard tissue and suggest malignancy. The Strain Ratio (quantitative elastography) is being calculated by comparing two different areas (A and B). Area A includes as much of the target lesion as possible. Area B is selected within a soft (red) reference area outside the target lesion. The result ($B/A = 141.7$) suggests malignancy; B: Shows the round, sharply demarcated and hypoechoic lymph node (white arrow). The endoscopic ultrasound-elastography was done using a Hitachi-Avius console with a radial scope EG-3630URK (from Pentax Medical).

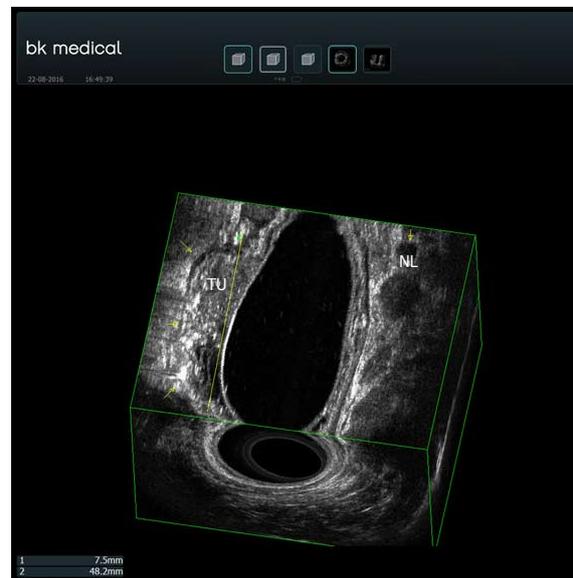


Figure 6 Rectal adenocarcinoma staging by 3D endoscopic ultrasound T1 N1. The yellow arrows on the left show the muscularis propria. The tumor invades up to the submucosa. A white submucosa plane can be seen between the tumor (TU) and the muscularis propria. The yellow arrow on the right shows a round lymph node. The 3D image was obtained using a transanal rigid probe with an ultrasound from bk medical.

of overstaging and 14% of understaging^[108,109]. Another limitation is that in 14% of RC there is a stricture that cannot be traversed by the echoendoscope, leading to an inaccurate T and N staging. The presence of a stricture decreases the EUS accuracy rate for T stage from 93% to 56%. When the T stages were analyzed separately, the accuracy was 76% for T1, 72% for T2, 91% for T3 and 67% for T4 stage. Moreover, there was an 11% of over-staging and 5% of under-staging errors^[110]. Ultrasound catheter probes can be used to compensate this limitation. A meta-analysis (10 studies, $n = 642$) showed a high performance using ultrasound catheter probes for T and N staging. The pooled sensitivity and specificity were for T1: 91% and 98%, T2: 78% and 94%, T3-T4: 97% and 90%, respectively. The sensitivity and specificity for N staging were 63% and 82%, respectively^[111]. Finally, the circumferential resection margin (CRM) is an important factor in predicting local recurrence. MRI has been described to

have a better overall accuracy compared to EUS (92% vs 84%) with similar NPV (97%), especially in mid-rectum^[112]. However, in low RC the accuracy in both modalities is similar (87%) with a NPV of 96%^[113].

New technologies

EUS elastography is a software application that can analyze the elastic properties of tissues (Figure 4). Harder tissue (usually malignant) appears blue which allows one to distinguish between adenocarcinomas and adenomas with high accuracy (94%)^[114]. It seems that EUS elastography is better in RC staging than EUS alone especially for early cancers^[115]. Contrast enhanced ultrasonography (CE-US) can be used to evaluate tumor

vascularity and response to antiangiogenic treatment^[116] (Figure 5). Computed parameters can be used to quantify tumor angiogenesis and measure vascularity changes after therapy^[117]. Finally, 3D-EUS development allows spatial display of rectal and perirectal anatomy^[112] (Figure 6). It improves accuracy for both T and N staging, better than EUS alone, especially in the middle third of the rectum^[118]. Published data shows that its accuracy for N stage improves from 65% to 85% and for T stage is 97.1% for T1, 94.3% for T2, 95.7% for T3 and 98.5% for T4^[119-121].

COLON CANCER

Despite improvements in EUS technology that allows a forward viewing, the EUS examination of the colon has proved to be less accurate for T and N staging (81% and 52.4% respectively)^[122]. This decrease is due to the difficulty in evaluating the proximal colon segments and bowel movement^[123]. Mini-probe EUS can be passed through the working channel of regular colonoscopes and can be used to evaluate lesions of the entire colon compensating for some of these limitations^[124].

ANAL CANCER

EUS is useful for assessing the involvement of anal sphincters in low rectal tumors and in the staging of anal squamous-cell carcinomas. Treatment decisions in anal cancer depends on sphincter invasion and EUS has an accuracy of 96%, sensitivity of 100%, specificity of 87% and NPV of 100% in evaluating it^[125,126]. Clinical staging of anal cancer tends to under-diagnose sphincter invasion^[127-129]. Most clinically classified T1-T2 patients will have T3 lesions under EUS evaluation^[129]. Giovannini *et al.*^[130] confirm this in a prospective multicenter study and recommend that in T1-T2 N0 tumors, a transrectal EUS should be performed. EUS can be used also to determine multimodality therapy response^[131]. A greater proportion of T1-T2 N0 lesions classified by EUS had a complete response to treatment than those classified by conventional clinical staging (94.5% vs 80%, respectively)^[130]. The use of 3D-EUS in anal carcinoma seems to add some benefits in perirectal lymph node and tumor invasion detection, when compared to standard EUS, but further studies are needed^[132].

CONCLUSION

Prognosis of patients with gastrointestinal cancer is strictly related to the stage of the disease at the time of diagnosis. Therefore, an accurate staging is crucial to decide the best treatment in each patient, because of the possibility of under-staging or over-staging, with subsequent mistreatments. CT scan, MRI, PET are the imaging methods that can give better information on distant disease. EUS has proven to be essential for loco-regional staging in pre-surgical evaluation. It reduces

the number of unnecessary surgeries, reduces local recurrences, improves survival outcomes and guides physicians in the development of the most appropriate therapeutic strategy. It has excellent sensitivity and specificity in accurately diagnosing T and N cancer stages. FNA substantially improves EUS outcomes by enabling tissue sampling, especially for N staging. New technologies, like elastography, contrast-enhancement EUS, high-frequency probes and 3D technology are also improving EUS accuracy. On the other hand, physicians should be warned that EUS has some limitations. EUS has low accuracy in restaging RC after treatment due to the difficulty in differentiating inflammation and tissue fibrosis from residual cancer. There is also some heterogeneity in the evidence currently available about EUS results in diagnosing superficial tumors (T1a) and LN in some situations.

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