

# Has the role of EUS in rectal cancer staging changed in the last decade?

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## ABSTRACT

The need for effective diagnosis, staging, and treatment of rectal cancer cannot be overstated. Accurate staging of rectal cancer has wide-ranging implications, including therapeutic strategy and prognosis. A change in stage may lead to the need for preoperative neoadjuvant therapy to decrease the risk of recurrence. The modalities commonly used for the primary staging of rectal cancer include EUS, computed tomography, and magnetic resonance imaging. EUS may be accompanied by the use of EUS-fine-needle aspiration to provide cytological confirmation. In this review, we take a deeper look into the role of EUS in the accurate staging of rectal cancer, how it compares to other modalities for the same, and how its role has changed in the last decade.

**Key words:** EUS, magnetic resonance imaging scan, magnetic resonance imaging, rectal cancer, staging

## INTRODUCTION

According to the American Cancer Society, 39,910 new cases of rectal cancer will be diagnosed in the United States in 2017.<sup>[1]</sup> Colorectal cancer is the third most common cancer diagnosed in both men and women.<sup>[1]</sup> Thus, the need for effective diagnosis, staging, and treatment of rectal cancer cannot be overstated. Accurate staging of rectal cancer has wide-ranging implications. Foremost is the choice of treatment strategy offered, which changes drastically with a change in the clinical stage of the patient.<sup>[2]</sup> While early lesions (cT1N0M0) with minimal invasion may be effectively treated with local resection with endoscopic polypectomy or transanal endoscopic microsurgery, 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 (cT3-4 or node-positive disease). Staging also gives important information regarding patient prognosis. Thus, accurate staging is the foundation on which an effective management plan for rectal cancer is built. Multiple modalities have been used for staging rectal cancer – computerized tomography (CT), magnetic resonance imaging (MRI), positron emission tomography, and EUS.<sup>[2]</sup> In this review, we take a deeper look into the role of EUS in the accurate staging of rectal cancer, and how this role has changed over the course of the last decade.

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**How to cite this article:** Uberoi AS, Bhutani MS. Has the role of EUS in rectal cancer staging changed in the last decade? *Endosc Ultrasound* 2018;7:366-70.

### Access this article online

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#### Website:

[www.eusjournal.com](http://www.eusjournal.com)

#### DOI:

10.4103/eus.eus\_36\_18

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**Received:** 2017-09-02; **Accepted:** 2018-08-09; **Published online:** 2018-12-06

## EUS FOR T-STAGING OF RECTAL CANCER

The normal appearance of the rectum on EUS is an echo pattern which consists of five layers.<sup>[3]</sup> The first and second layers correspond to the rectal mucosa, the third layer corresponds to the submucosa, the fourth layer is the muscularis propria, and the outermost (fifth) layer is the adventitia. Rectal cancers are seen on EUS as hypoechoic masses which are seen to disrupt this normal echo pattern of the rectum. T1 lesions are limited to the mucosa and submucosa and thus do not extend beyond the first three echo layers seen on EUS. T2 lesions are seen to extend up to but not penetrate through the fourth hypoechoic layer (which corresponds to the muscularis propria). T3 lesions invade through the muscularis and may even extend beyond the five echo layers into the perirectal space. A T4 lesion invades the visceral peritoneum or involves the adjacent organs such as the prostate, bladder, seminal vesicles, or vagina.

The accuracy of EUS for T-staging in reports has varied from as low as 63% up to a highest report of 96%.<sup>[4,5]</sup> In the largest meta-analysis to date, Puli *et al.* evaluated data from 42 studies ( $N = 5039$ ) which compared EUS T-stage with that determined by surgical histopathology.<sup>[6]</sup> The authors calculated the pooled sensitivity and specificity of EUS to be 87.8% (95% confidence interval [CI]: 85.3%–90.0%) and 98.3% (95% CI: 97.8%–98.7%), respectively, for T1 lesions; 80.5% (95% CI: 77.9%–82.0%) and 95.6% (95% CI: 94.9%–96.3%), respectively, for T2 lesions; 96.4% (95% CI: 95.4%–97.2%) and 90.6% (95% CI: 89.5%–91.7%), respectively, for T3 lesions; and 95.4% (95% CI: 92.4%–97.5%) and 98.3% (95% CI: 97.8%–98.7%), respectively, for T4 cancer. The authors concluded that EUS is accurate for the T-staging of rectal cancer.

These findings have not been supported by subsequent reviews. Marusch *et al.* conducted a large, 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.<sup>[7]</sup> This was done by calculating the degree of correspondence between EUS assessed T-stage (uT) and the T-stage on histopathological examination (pT). The value of this correspondence was calculated by the authors to be 64.7% (95% CI: 63.6%–65.8%). Of the 35.3% of cases, when the T-stage was not found to correspond, 18% (95% CI:

17.1%–18.9%) was due to understaging by EUS and 17.3% (95% CI: 16.4%–18.2%) was due to the EUS overstaging cancer. T2 and T4 lesions were reported to have a lower rate of correlation between EUS and histopathological T-stage than T1 and T3 lesions. This study also sought to compare the hospital EUS volume with the degree of uT-pT correspondence. It was seen that uT-pT correspondence was 63.2% (95% CI: 61.5%–64.9%) for centers which performed  $\leq 10$  EUS per year, 64.6% (95% CI: 62.9%–66.2%) for those performing 11–30 EUS per year, and 73.1% (95% CI: 69.4%–76.5%) for those with a EUS caseload 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.

While any change in T-stage has significance to patient prognosis, a change in T-stage at the threshold for primary surgical resection (without the need for neoadjuvant therapy) has enormous implications in patient management. Ahuja *et al.* aimed to assess the accuracy of EUS at this important branch point in therapeutic strategy by calculating the negative predictive value (NPV) of EUS for T2 disease.<sup>[8]</sup> As pT1 lesions overstaged as uT2 would not have any effect on the treatment strategy (no need for neoadjuvant therapy in both T1 and T2), these cases were not regarded to be incorrectly staged. Using this methodology, the authors calculated that EUS had an NPV of 0.837 (95% CI: 0.742%–0.908%) for T-stage. In 16.3% of cases, EUS understaged T3 disease as T2, leading to an incorrect treatment strategy. The authors concluded that this rate was comparable to the other imaging modality in these patients, *i.e.*, pelvic MRI.

## EUS FOR N-STAGING OF RECTAL CANCER

The N-staging of rectal cancer is determined by assessing the perirectal lymph nodes for changes seen in malignant infiltration. A thorough lymph node survey is performed from the anal verge up to the level of the iliac vessels approximately 25–30 cm from the dentate line. These nodes are usually round and hypoechoic and have a regular border. Although various studies have described different size cutoffs 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.<sup>[9,10]</sup> The presence of 1–3 malignant appearing

nodes is considered as N1 disease and 4 or more nodes as N2 disease.

Puli *et al.* conducted a meta-analysis to determine the accuracy of EUS for the N-staging of rectal cancer ( $N = 2732$ ).<sup>[11]</sup> They determined the pooled sensitivity of this modality to be 73.2% (95% CI: 70.6%–75.6%) and pooled specificity to be 75.8% (95% CI: 73.5%–78.0%). The positive likelihood ratio was 2.84 (95% CI: 2.16%–3.72%) and negative likelihood ratio was 0.42 (95% CI: 0.33%–0.52%). 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.

Gleeson *et al.* performed a prospective study to assess the accuracy of the conventionally used echo features of lymph nodes (hypoechoic, round, smooth borders, short axis  $\geq 10$  mm), along with nodal dimensions to predict malignant invasion of lymph nodes.<sup>[12]</sup> This study also aimed to assess if a cutoff or threshold number of positive criteria could be used to accurately predict the involvement of lymph nodes. The results of this study showed that only two nodal features could adequately predict malignancy – short-axis length  $\geq 5$  mm (odds ratio = 2.7; 95% CI: 1.3%–6.1%;  $P = 0.009$ ) and hypoechoic appearance (odds ratio = 3.8; 95% CI: 1.4%–13.8%;  $P = 0.017$ ). The nodal dimensions with the highest accuracy were short axis of 6 mm (sensitivity 59%, specificity 90%) and long axis of 9 mm (sensitivity 46%, specificity 95%). The authors 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. Another challenge in the identification of nodes with EUS is the inability to visualize nodes that are outside the range of the transducer. Thus, N-staging of rectal cancer remains to be an area of uncertainty.

### EUS-FNA

EUS-FNA may be used in addition to visual characteristics of lymph nodes to accurately identify nodal involvement in rectal cancer. While it theoretically provides the prospect of increased accuracy due to the cytological confirmation of malignant changes, various reports have had conflicting results. Some reports have asserted that EUS-FNA is a useful tool for the

accurate staging of rectal cancer and can improve the accuracy of EUS alone for nodal staging.<sup>[13–15]</sup> The use of EUS-FNA in the staging of rectal cancer patients was associated with a reduced recurrence risk as compared to staging by CT scan.<sup>[16]</sup> In another report, Harewood *et al.* reported that the addition of FNA did not significantly change management in patients who were N-staged with radiographic characteristics alone.<sup>[17]</sup> This was due to the fact that in patients with T3 or more advanced lesions, the detection of previously undiagnosed nodal disease would not alter therapeutic strategy as these patients would receive neoadjuvant chemoradiation regardless of N-stage. 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) as this would lead to a high false-positive rate, along with the possibility of potential seeding of nodes with malignant cells.

### EUS VERSUS COMPUTERIZED TOMOGRAPHY AND MAGNETIC RESONANCE IMAGING

Bipat *et al.* performed a meta-analysis in 2004 to compare the accuracy of EUS, CT, and MRI for the staging of rectal cancer.<sup>[18]</sup> The authors reported that EUS was superior to CT and MRI for the T-staging of rectal cancer and comparable to these modalities for N-staging. However, 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 of rectal cancer has vastly improved.<sup>[19–22]</sup> Specifically, MRI has been proven to be the most accurate modality for the prediction of the involvement of the circumferential resection margin (CRM), which is an extremely important prognostic factor as well as important in the surgical planning before TME.<sup>[22,23]</sup> Thus, MRI is preferred over EUS in locally advanced cases (T3/T4) which require a more detailed evaluation of the resection plane and the CRM. MRI also has more utility over EUS in stenotic lesions where the EUS probe may not be passed across the lesion.<sup>[24]</sup> On the other hand, MRI is inferior to EUS for early lesions as differentiating between T1 and T2 lesions is challenging

with MRI due to limited visualization of the rectal submucosa.<sup>[18,25]</sup> This may be of importance in choosing the resection strategy in early cases. Furthermore, polypoid morphology of the tumor is associated with decreased accuracy of MRI for T-staging.<sup>[24]</sup> Thus, choosing the appropriate imaging modality has to take multiple factors into consideration, including clinical picture, availability of experienced personnel, treatment strategy, and cost. CT scanning plays an important role in the assessment of systemic spread of rectal cancer and has a limited role in locoregional staging.

While literature suggests that EUS and MRI are comparable for the staging of rectal cancer, in the author's (MSB) personal experience at a tertiary cancer center in the developed world, the number of cases referred by colorectal surgeons and oncologists for staging by EUS has steadily declined over the past decade. This may be attributed to several factors. The primary reason is the advantages of high-quality latest generation MRI for determination of CRM, surgical planning, and providing T-stage information for T3/T4 cases. Only selected cases are referred now when after the MRI, determination of T1/T2 stage is needed, or there is a node seen on MRI, EUS-FNA of which is desired by the surgical or medical/radiation oncologists. While improvements in MRI technology have made it comparable or even superior to EUS in certain clinical circumstances, it is also a more convenient option in many practical settings. The availability of sufficiently experienced personnel for EUS may be a limiting factor in many practices, whereas radiology services may be more widely available. Furthermore, MRI is less invasive for the patient while EUS involves some degree of discomfort. However, there may be countries and hospitals where newer MRI technology is not available, but there is an experienced endosonographer who performs rectal EUS routinely, and EUS may be a better option there. Thus, the decision is not straightforward and must take into account the variables above.

### **ROLE OF EUS IN RESTAGING AFTER CHEMOTHERAPY AND RADIATION**

Restaging of locally advanced rectal cancer after neoadjuvant chemoradiation is useful to tailor therapeutic strategy, allowing patients with good response to forego the morbidity and loss of function associated with more extensive procedures. However, multiple studies have reported that for this purpose,

EUS lacks the accuracy it shows in primary staging.<sup>[26-31]</sup> Changes seen in the peritumoral region because of the effects of chemoradiation such as edema, inflammation, necrosis, and fibrosis lead to a hypoechoic appearance which mimics the primary tumor, leading to frequent overstaging. Thus, EUS is not generally recommended in the routine restaging of rectal cancer after preoperative therapy.

### **ENHANCED EUS TECHNIQUES FOR RECTAL CANCER**

EUS elastography is an enhanced technique which can be utilized to quantify the relative elasticity or hardness of tissues, which in turn allows us to differentiate and delineate benign areas (more elastic) from malignant areas (less elastic). Software applications can be used to quantify these data by either forming color-coded histograms or calculating a strain ratio by comparing elasticity of a particular region of interest with a reference value. While studies have shown that elastography can be an effective modality to differentiate benign rectal adenomas from malignant tumors, the exact role of this technique in the staging of rectal cancer is yet to be studied and reported.<sup>[32]</sup>

Contrast-enhanced EUS is another development which has been used to visualize and quantify tumor vascularity. This is done with the help of microbubbles which are used as intravenous ultrasound contrast agents and estimation of perfusion levels with the help of objective parameters such as area under the curve in the time-intensity curve. While this data can be used to assess response to antiangiogenic therapy, the routine application of this modality for the staging of rectal cancer is not yet mainstream and standardized.<sup>[33]</sup>

### **CONCLUSION**

Accurate staging of rectal cancer is essential to make appropriate therapeutic decisions. EUS is accurate for the locoregional staging of these patients and has been shown to perform favorably as compared to other modalities for early lesions. Performance of EUS depends on the experience of personnel and the volume of cases performed at the center, leading to real-world results which may not match those reported in literature in the hands of less experienced endosonographers. Selection of staging modality should be individualized according to the clinical picture, and



the use of EUS may be complemented with the use of other modalities such as CT for assessment of systemic disease and MRI for the involvement of the CMR. Recent dramatic advances in MRI technology make it the preferred initial local staging choice at many centers, with EUS reserved for determination of T1/T2 staging and when EUS-FNA is desired.

### Financial support and sponsorship

Nil.

### Conflicts of interest

There are no conflicts of interest.

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