

# Endoscopic Ultrasound: Current Role and Future Perspectives in Managing Rectal Cancer Patients

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## Abstract

As therapeutic regimens for rectal cancer have seen considerable changes, an accurate staging is mandatory for choosing the adequate strategy. Locoregional staging is the decisive factor in selecting patients for neoadjuvant chemoradiation therapy and for determining the extent of surgery. Endoscopic ultrasound (endorectal ultrasound - ERUS) is a very effective method for assessing the local extent of rectal cancer, especially regarding the depth of tumor infiltration. Although a significant limitation is represented by its lower accuracy for diagnosis of lymph node metastases, this is still a point of concern for other imaging tests as well. In this review we report the current data on ERUS, presenting both its advantages and limitations, and making a comparison to other staging methods. Recent developments of the technology that might enhance staging accuracy are also discussed.

## Key words

Endoscopic ultrasound – rectal cancer – staging accuracy – three-dimensional endoscopic ultrasound – elastography.

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## Introduction

Colorectal cancer represents a global health burden being the third most common cancer diagnosed in males and the second in females. Although most cases are diagnosed in developed countries, incidence rates are rapidly increasing in areas of previously low risk [1]. In Romania 8,696 new cancer cases and 5,178 deaths are estimated to have occurred in 2008 for both sexes [2]. About 35% of the colorectal

cancers develop in the rectum, i.e. 15-25/100,000 per year, with a mortality rate between 4-10/100,000 per year [3].

The management of rectal cancer has seen considerable advancements, and an accurate pre-therapeutic staging is mandatory in deciding the optimal strategy of a multidisciplinary care plan. It helps in determining a patient's prognosis which is closely related to the depth of tumoral invasion (T stage) and the number of involved lymph nodes (N stage). Staging is the decisive factor in guiding the treatment by selecting patients eligible for preoperative therapy and determining the extent of surgery [4]. Current methods for preoperative staging of rectal cancer patients include computed tomography (CT), endorectal ultrasonography (ERUS), magnetic resonance imaging (MRI) and positron emission tomography (PET). The option for one investigation or another is based on availability and local expertise [5].

In this report, we review the current roles and future perspectives of ERUS in the management of rectal malignancies, outlining its advantages and its limitations as well.

## Endorectal ultrasound

Since the initial report on the technique in the early 1980s [6, 7], endoscopic ultrasound has been widely used in daily clinical practice with significant impact on diagnosing and staging malignancies of the gastrointestinal tract and the surrounding structures. For rectal cancer staging ERUS was first reported in 1985, with promising results [8] and nowadays it is accepted as the method of choice for the initial evaluation of rectal tumors, being considered a fast, safe and highly accurate staging tool [9].

## Technique and interpretation

An accurate ERUS imaging implies a properly cleaned rectum in order to avoid artifacts. For this purpose laxative enemas are usually sufficient although standard colonoscopy preparation could enhance the examination and allow searching for synchronous lesions during the same endoscopic session. Generally it is a well tolerated procedure that does

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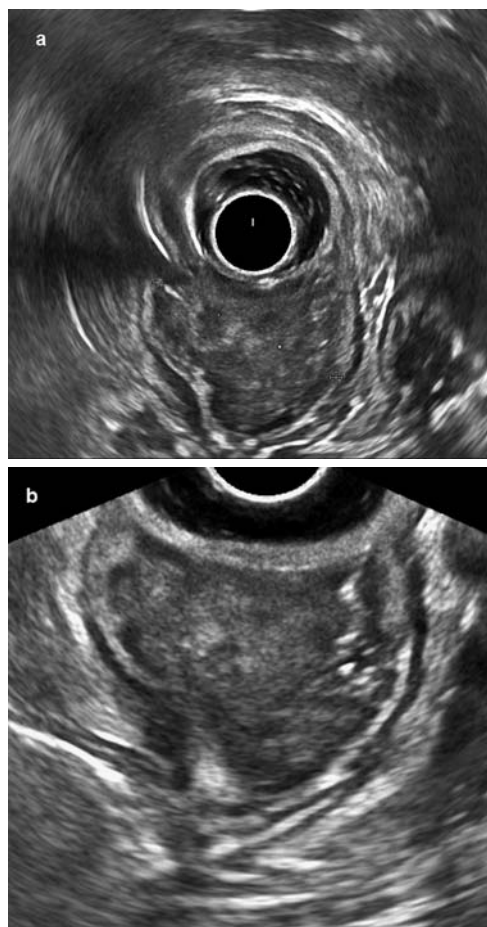
not necessitate sedation of the patient [9]. The examination may be performed with a flexible echoendoscope or a rigid probe with a radial transducer. Whenever tissue sampling is expected a linear echoendoscope should be used as it also enables fine-needle aspiration from the site of interest [9, 10]. Another option would be to use high-frequency miniprobes that can easily be passed through the working channel of standard endoscopes. These are the best option for obstructive tumors that cannot be assessed with a rigid probe. The procedure begins with a digital rectal examination and also, prior to ERUS, at least a rectosigmoidoscopy should be performed for a clear description of tumor size and location, with note on the distance from the anal verge. With the patient in left lateral position, the transducer, covered in a water-filled balloon to avoid air artifacts, is inserted and advanced into the rectum [11]. Imaging can be performed at variable ultrasound frequencies, between 5 to 15 MHz, depending on the information we are seeking. While higher frequencies provide better resolution with clear delineation of the rectal wall layers, assessment of the perirectal tissue and lymph nodes invasion needs lower ultrasound frequencies [12, 13].

At ERUS examination the rectal wall appears as five alternating hyper- and hypoechoic layers reproducing the anatomic layers. The inner hyperechoic line corresponds to the interface between the superficial mucosa and the water-filled balloon. The next hypoechoic layer stands for the mucosa and muscularis mucosae. The third layer is hyperechoic, representing the submucosa. The fourth (hypoechoic) layer is the muscularis propria, and the last hyperechoic line represents the interface between the rectal wall and the perirectal fat [9, 11]. This bedding is more or less altered by rectal tumor infiltration imaged as hypoechoic lesions (Fig. 1a,b). Assessment of the depth of penetration (T stage) follows the international TNM classification and the ultrasonographic staging is suggested by the prefix ‘u’ [13]. For N staging, involvement is usually suspected if a lymph node is over 5 mm in diameter, round and hypoechoic, features which may differentiate them from inflammatory nodes [11] (Fig. 2). Furthermore, a tissue diagnosis of malignancy can be established by performing EUS-FNA.

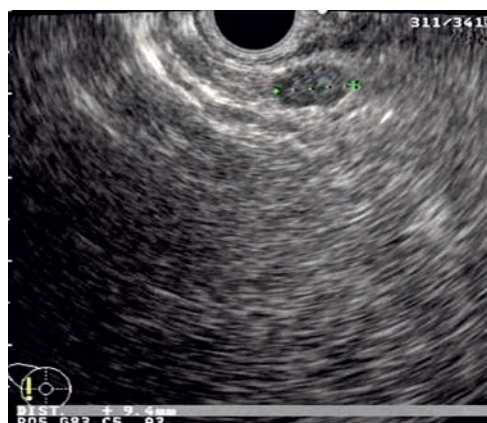
### T staging

The tumor depth of invasion into the rectal wall and surrounding structures is a very strong predictor of a patient’s survival and is essential for guiding the treatment plan. The reported results of accuracy for T staging using ERUS are variable in the literature.

In a retrospective study over a 10 year experience, the overall accuracy for classifying T category was 69% [14]. Validation of the ERUS staging was made by comparison with the pathologic stage, based on examination of the resection specimens. T3 tumors were most accurately staged (86%), while differentiating between T1 and T2 tumors was found to be especially difficult. More frequently, tumors were overstaged (19%), while 12% of cases proved to be



**Fig 1.** a. ERUS image of a rectal cancer showing a hypoechoic mass that penetrates the submucosa; b. further examination depicts the tumor invading through the muscularis propria into the perirectal fat (uT2).



**Fig 2.** ERUS identifying a round perirectal lymph node, with hypoechoic appearance, of approximately 1 cm diameter (uN1).

understaged. The authors also noted a high inter-observer variability, the accuracy being higher for an experienced examiner. When comparing the performance of the method at different ultrasound frequencies the 10-MHz scanner was more accurate than the 7.5-MHz scanner only for T1 tumors

(71% vs 36%). Another group reported an 81% accuracy for preoperative T-staging on a series of 424 patients, when examination was performed by highly experienced surgeons [15]. In a prospective multicenter study on the use of ERUS for pre-therapeutic staging in clinical practice, the accuracy for all T-categories was 65.8%, less than previously published data, the main reason being considered the moderate experience of the investigators [16]. The highest sensitivity was found again for T3 tumors (74.9%). Recently, a meta-analysis reviewing articles published between 1980 and 2008 showed high sensitivity for ERUS in evaluating tumor invasion (88-95%), with the best results obtained for more advanced disease [17].

An important consideration in staging rectal cancer is to distinguish between early and advanced lesions, thus deciding when endoscopic treatment is deemed to be curative. In a prospective study, ERUS enabled selection of patients with rectal neoplasia that were suitable for local excision with 95% accuracy [18]. Another group reported 96% sensitivity, 85% specificity, and 94% accuracy for ERUS in differentiating early from advanced rectal cancers [19]. Also, a recent meta-analysis strongly recommended ERUS for staging early tumors, showing excellent sensitivity and specificity in diagnosing T0 category (97.3%, 96.3% respectively) [20].

Although results may vary, common observations arise from the previously mentioned studies. The accuracy of endorectal ultrasound staging varies with the T category, uT2 lesions being the least accurately assessed [13]. This is more often due to overstaging of the tumor. Also, the technique is highly operator dependent and requires experience with the probe [11, 21]. In patients with stenosing tumors staging may be suboptimal as the ERUS scope might not be able to pass the stenosis. For these cases, although they usually represent advanced tumors, catheter ultrasound probes, as mentioned above, can be a solution [22], as well as dilation of the tumor, followed by staging.

## N staging

A significant drawback in using ERUS for routine staging of rectal cancer is its lower accuracy in assessing lymph node involvement, ranging from 70 to 75% [22, 23]. A retrospective study found unsatisfactory results, with overall accuracy of 68% in classifying the N category, 52% sensitivity and 82% specificity [14]. This came to confirm previous results of another group reporting 10 year experience with 64% accuracy in diagnosing nodal metastases [24]. A review of the data published in 35 studies, over a period of more than two decades, resulted in a pooled sensitivity of 73.2% and specificity of 75.8% for ERUS in assessing nodal involvement [25]. Another conclusion of this meta-analysis was that ERUS could more accurately exclude nodal invasion than confirm it.

One cause of misinterpretation leading to poor results in diagnosing nodal status by ERUS is the presence of reactive inflammatory nodes. These are difficult to distinguish from

malignant lymph nodes based only on the echo features and so false-positive results may follow. The size criterion is also a particular problem. While positive nodes are generally considered to be round, hypoechoic and over 5 mm in diameter [22, 26], metastatic foci have been reported in approximately 18% of nodes smaller than 5 mm [27, 28]. An interesting study found the incidence of metastases to be 9.5% in nodes with  $\leq 2$  mm in short axis diameter, 47% for 3 to 5 mm nodes, and 87% for  $\geq 6$  mm diameter [29].

A more recent study examined the accuracy of ERUS for determining nodal invasion in correlation to the depth of infiltration of the primary tumor. They found that for less invasive tumors the size of the lymph nodes and metastatic deposits as well as the accuracy of the method in detecting them decreased [30]. The ability of ERUS to correctly stage lymph node status dropped significantly from 84% for pT3 tumors to 48% for pT1 tumors, in the latter case the median size of the nodes and of the metastatic deposits being 3.3 mm, and 0.3 mm, respectively. A conclusion arising from this study was that early stage tumors have small metastatic deposits, more likely to be missed by ERUS. This may be the cause of pelvic recurrence seen after local excision. And what comes to mind is the question whether it is wise to select patients with early cancer for local excision based on ERUS only. One suggested solution was to decrease the nodal size criterion. But while this might raise the method's sensitivity for detecting nodal disease, it would also lead to lower accuracy and specificity overall. When considering the cutoff of 5 mm, ERUS sensitivity, specificity and accuracy for diagnosing nodal involvement in T1 lesions were found to be 38%, 94% and 89% respectively, values that changed when using a 3 mm cutoff to 75%, 49%, and 53%, respectively [13, 30, 31]. ERUS-guided fine needle aspiration (FNA) might increase the specificity in nodal staging by offering histological confirmation. However the results published so far are contradictory and need further extensive studies for validation of the technique [32-34].

It is clear that using the diameter criterion is not enough for assessing nodal disease [29]. A recent study aimed to identify a combination of echo features that could predict with high accuracy lymph node metastases in rectal cancer patients [35]. They found hypoechoic appearance and short axis length  $\geq 5$  mm to be the only features that could independently predict malignant infiltration, but still with insufficient accuracy. No other conventional echo features could accurately distinguish benign from malignant nodes, except when all were present, this being the case of only 23% of the node-positive cancers found. They concluded that overall experience was more reliable than conventional ultrasound criteria and that FNA was needed to identify nodal status when making critical therapeutic decisions.

Another drawback when using ERUS is its limited field of view, being unable to analyze lymph nodes out of the transducer's range. This is a problem encountered especially for rigid rectal probes which cannot be used to evaluate the iliac area for lymph nodes. These are particularly important to assess as they are considered M1 stage and imply a



different therapeutic approach [9, 22]. Of the node-positive lower rectal cancers, about 28% had iliac adenopathy in one study, 6% of patients having only positive iliac nodes [36, 37]. For these patients flexible echoendoscopes allow deeper insertion and evaluation of the iliac region. Furthermore, this is where ERUS-FNA, possible only with linear transducers, might improve rectal cancer staging. In one study including 457 patients, FNA was used to diagnose nonperitumoral lymph nodes visualized by ERUS. From 32 patients with suspicious iliac lymph nodes, FNA confirmed malignancy for 15 (47%) and changed their course of therapy. On the other hand, CT detected iliac adenopathy in only 7 of the 15 cases found positive by ERUS-FNA [38]. These data argue for the routine assessment of iliac nodes with ERUS when staging rectal cancer patients [22].

### A parallel to other staging methods

Computed tomography (CT), although widely available, is unable to distinguish the different rectal wall layers. Therefore, while it is still considered the standard of care for detection of metastatic disease, it may not be the investigation of choice for local staging of rectal cancer patients [5]. In a study comparing the efficacy of ERUS and spiral CT, ERUS proved once again to be superior in staging the depth of tumor infiltration, although there was no statistically significant difference between the two methods for diagnosing nodal metastases. The accuracy for ERUS versus spiral CT was 84.6% vs. 70.5% for T staging, and 64.1% vs. 61.5% for N staging [39].

A review of 31 papers published over a period of two decades evaluated the use of ERUS and MRI for preoperative staging of rectal tumors. They found an overall accuracy for ERUS of 82% for T category, the method being most accurate for early localized cancers. MRI was considered more useful for advanced disease, providing clear definition of the mesorectal fascia. Its accuracy for assessing the depth of tumor penetration was 76% for all categories. Both methods were found similarly accurate in assessing the nodal invasion [40].

Another group reviewed 83 studies and reported the effectiveness of all three methods. The results showed that ERUS was the most accurate for assessing tumor wall penetration. When analyzing MRI with an endorectal coil the results were similar to ERUS for T staging, but for nodal involvement it appeared to be the most effective method [41]. A more recent meta-analysis found ERUS to be a better imaging test for local staging as compared to CT or MRI. For lymph node involvement, all three techniques showed similar results, with low sensitivity values, still representing a point of concern [42].

Although endorectal MRI shows comparable accuracy with ERUS for local staging, it also shares the same technical limitations, including poor resolution of perirectal structures, and difficulty in staging stenosing tumors. On the other hand, MRI with a pelvic phased-array coil is noninvasive, has improved spatial resolution, and recent studies have shown

promising results for staging rectal cancer [43, 44].

While it is clear that all imaging tests for rectal cancer need improvement, regarding cost-effectiveness the combination of abdominal CT and ERUS seems to be the best approach as compared to abdominal CT and pelvic MRI, and CT alone [22, 34]. However, instead of searching for the best technique, we should consider them complementary and use them for the best interests of the patient, certainly based on previous experience and availability.

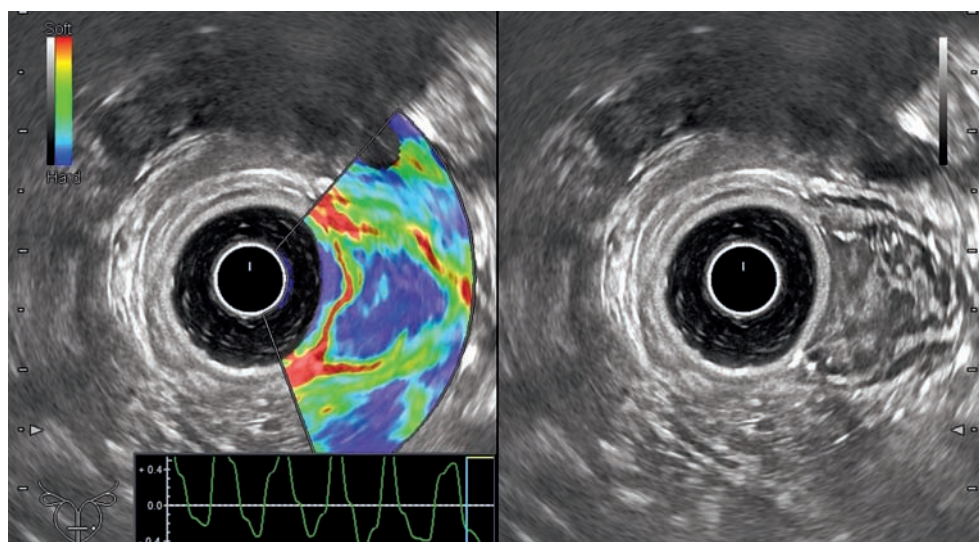
### Restaging after neoadjuvant chemoradiation therapy

The staging accuracy of ERUS after neoadjuvant therapy is compromised by the effects of chemoradiation: peritumoral inflammation, edema, necrosis, and fibrosis [13, 22, 45]. Postradiation changes are difficult to distinguish from the residual tumor and thus poor staging results mainly from overstaging. One study including 82 patients with advanced rectal cancer who were restaged by ERUS after concurrent 5-fluorouracil and radiotherapy reported an overall accuracy for post chemoradiation T staging of only 48%, with 14% of cases being understaged and 38% overstaged. ERUS was able to predict complete response to therapy in 10 of 16 patients (63%). For nodal status the accuracy was 77% [46]. Another group compared the accuracy of ERUS staging for rectal cancer in patients undergoing surgery without (group I), and following preoperative chemoradiation (group II). ERUS was proven once again less accurate for T staging after chemoradiation. The method was able to predict complete response (T0N0) in only 50% of cases [47].

Recently, ERUS and MRI were comparatively used to evaluate rectal cancer patients after neoadjuvant therapy, validating the findings with histopathology from surgical specimens. Both ERUS and MRI showed unsatisfactory results for assessing residual tumors, being able to correctly classify 46%, and 44% of patients, respectively. For nodal involvement the accuracy was 69%, and 62%, respectively [48]. While for the initial evaluation ERUS and MRI are both accurate methods, neither seems reliable for restaging after chemoradiation. This is an area where improved imaging techniques and possibly the addition of functional imaging are required for better staging and prediction of response to therapy [37]. Recent studies have found positron emission tomography (PET) to be a promising tool in evaluating the effectiveness of neoadjuvant therapy for rectal cancer, demonstrating high predictive value. However, further studies are still required to define the best interval and parameters to use for evaluation [49, 50].

### Recent developments and future perspectives

The addition and improvement of recent technologies have made endoscopic ultrasound a test of significant clinical impact in digestive diseases, regarding diagnosis, staging and prognosis stratification [51]. These novel techniques are applicable to rectal tumors, pending further clinical studies.



**Fig 3.** Elastography image during ERUS of a rectal cancer showing a hard mass that invades the muscularis propria (uT2).

Three-dimensional ERUS (3D-ERUS) enhances the understanding of the spatial relations of rectal tumors resulting in improved staging and assessment of resectability. It can be used either with radial or linear transducers. Three-dimensional reconstruction may be more easily achieved with radial than with linear endoscopic ultrasound where the manual guidance and angulations of the transducer may lead to artifacts [52].

Thus, 3D-ERUS was found to be more accurate than two-dimensional ERUS and CT for staging rectal cancer. The accuracy of 3D-ERUS, 2D-ERUS and CT for assessing the depth of tumor infiltration was 78%, 69%, and 57%, respectively, while for evaluating nodal involvement it was 65%, 56%, and 53%, respectively. The most frequent causes of misinterpretation were the examiner errors. 3D-ERUS provided more information on the depth of invasion, revealing conical protrusions along the deep border of the tumor that correlated well with the histological findings in regard to the grade of infiltration, more advanced T-stage and nodal metastases [28]. A dedicated software program facilitates the manipulation of the rectal probe and makes 3D reconstruction easier. Such 3D images have proved a better definition of the mesorectal margins, thus overcoming one of the limits of two-dimensional ultrasound scans [53]. 3D-ERUS could assist endoscopic mucosal resections of early tumors for a safer and more effective procedure [54]. Accurate volumetric measurements are possible with this technique and may be used to predict response after chemoradiation therapy [52].

Elastography represents a recent development in endoscopic ultrasound that examines the elastic properties of tissues and thus might be able to differentiate malignant lesions from fibrous and benign tissue [55]. A preliminary report showed that elastography combined with ERUS improved the T-staging accuracy for rectal cancer [48, 56]. As a technique that simulates virtual palpation it might identify the lymph nodes most probable to be malignant and lead ERUS-FNA to

an enhanced diagnostic accuracy [51] (Fig. 3).

Contrast enhanced endoscopic ultrasound is a state-of-the-art imaging technique that uses blood-pool contrast agents as Doppler signal enhancers to assess tumor perfusion [51]. Although this technology has not been yet reported for the evaluation of colorectal cancer it might be a more accessible functional imaging test for predicting response to neoadjuvant therapy and especially antiangiogenesis treatment. In addition to the high resolution, it might offer information regarding changes in tumor vascularity during the same examination.

## Conclusions

Endoscopic ultrasound has proved to be an accurate method for the local staging of rectal cancer. Although it still has its limits, a wider use in clinical practice will lead to improved results. Furthermore, novel technologies such as 3D-ERUS, elastography, and contrast enhancement might bring additional information, increasing diagnostic accuracy of ERUS and expanding its roles in the complex management of rectal cancer patients.

## Conflicts of interest

Nothing to declare.

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