ORIGINAL CONTRIBUTION

Accuracy of Endoscopic Ultrasound to Assess Tumor Response After Neoadjuvant Treatment in Rectal Cancer: Can We Trust the Findings?

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BACKGROUND: The finding that some rectal cancers respond to neoadjuvant chemoradiation is broadening new surgical options for the treatment of some of these tumors that, until now, required a total mesorectal excision. Nevertheless, a fine match between clinical and pathological response is required when planning conservative surgical approaches.

OBJECTIVE: This study aims to prospectively validate the use of endoscopic ultrasound as a predictor of clinical and pathological tumor response in patients with locally advanced rectal cancer.

DESIGN: This is an observational study of a cohort of patients undergoing chemoradiation followed by surgery.

SETTINGS: This study was conducted at a tertiary medical center.

PATIENTS: A total of 235 consecutive patients who underwent chemoradiation followed by surgery at a single institution during a 7-year period were included.

MAIN OUTCOME MEASURES: All tumors were staged and restaged at 4 to 6 weeks after neoadjuvant treatment. Downsizing and downstaging were calculated between the initial and posttreatment measures and correlated to the pathological stage. The accuracy of endoscopic ultrasound to predict response was determined.

RESULTS: Findings after chemoradiation showed T-downstaging in 54 patients (23%) and N-downstaging in 110 (47%). Overstaging occurred in 88 (37%) patients and was more commonly observed than understaging (21 patients; 9%). Related to the pathological report, endoscopic ultrasound correctly matched the T stage in 54% and the N stage in 75% of tumors. Sensitivity, specificity, and positive and negative predictive values to predict nodal involvement were 39%, 91%, 67%, and 76%. Accuracy was not influenced by such factors as age, distance of the tumor from the anal verge, or time to surgery.

LIMITATIONS: This study was limited by the lack of comparison with other imaging methods.

CONCLUSIONS: Endoscopic ultrasound allows prediction of involved lymph nodes in 75% of the cases; however, 1 in 5 patients are missclassified as uN0 after neoadjuvant treatment. In our point of view, this percentage is too high to rely only on this diagnostic modality to support a "wait and see" approach.

KEY WORDS: Rectal cancer; Neoadjuvant chemoradiation therapy; Response assessment.

Modern treatment of locally advanced rectal cancer (stage II or III), combining total mesorectal excision (TME) with neoadjuvant chemoradiation (CRT), results in excellent local tumor control with an increased proportion of sphincter-preserving surgeries, and

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possibly improved long-term survival.[1] In addition, the proportion of patients who will have a pathological complete response ranges from 9% to 56% between series.[2] The finding that some rectal cancers achieve downstaging and/or downsizing after CRT is broadening to the field of less invasive procedures such as transanal local excision,[3,4] or perhaps no surgery at all (known as the "wait and see" approach).[5]

Before attempting any conservative approach in rectal cancer after CRT, surgeons need to be able to precisely assess whether there is residual tumor or fibrosis in the bowel wall and whether the regional lymph nodes are involved. Although there is a lack of consensus on which is the best assessment methodology, endoscopic ultrasound (EUS) has become the most common diagnostic modality used by most groups to plan conservative strategies in rectal cancer after CRT.[6] However, it's well known that radiation tissue changes, associated tumor fibrosis, and lymph node sterilization can lead to misinterpretation of EUS images and a decrease in accuracy rates when restaging the tumor after CRT.[7] In addition, EUS is an operator-dependent procedure and differences in accuracy rates have been observed when various operators or nonskilled hands perform the examinations.[8,9] For all these reasons, we believe that it is controversial whether clinical tumor regression should be considered as a true predictor of pathological response.

The present study aims to prospectively validate the use of EUS as a predictor of clinical and pathological tumor response in a cohort of patients with locally advanced rectal cancer treated by CRT followed by TME. Factors associated with the accuracy of EUS in restaging rectal cancer after CRT were also elucidated.

MATERIALS AND METHODS

The study included 235 consecutive patients with locally advanced rectal adenocarcinoma who underwent CRT followed by TME at a colorectal unit in a tertiary center (Clinica Universidad de Navarra, Spain) between March 1, 2003 and March 1, 2010. The study was conducted after obtaining approval from the local institutional review board committee.

Initial staging was performed in all cases by digital rectal examination, colonoscopy, total-body CT scan, and EUS. Patients with stage IV disease at initial diagnosis were excluded from the study. Demographic and patient baseline characteristics were obtained by reviewing the electronic medical records. All patients received preoperative CRT, which consisted of external beam pelvic radiation (50.4 Gy) and 5-fluoruracil/leucovorin-based chemotherapy or intensity-modulated radiation therapy (47.5 Gy) combined with capecitabine/oxaliplatin. After completing CRT, all patients underwent radical resection (low anterior resection, abdominoperineal resection, or Hartmann resection) according to the principles of the TME technique.[10] The type of surgery was indicated based on the initial EUS staging, independently of the uTN status after CRT, and without additional biopsies.

Patients were consented to be restaged by EUS before CRT and before surgery (the day before in all cases). The same experienced endoscopist (J.C.S.) performed all explorations using a flexible endoscope (GF-UM 160/GF-UE, Olympus Medical Systems, Germany) with a 5- to 20-MHz transducer that gives a 360° rotating image of the tumor and the mesorectum. Frequencies were modified as needed to obtain a high-quality resolution during the explorations. Depth of tumor invasion into rectal wall (T stage) and lymph node involvement (N stage) were determined based on TNM stage classification developed by the American Joint Committee on Cancer. EUS assessment of tumor infiltration (uT) was based on the following criteria: uT0, absence of a hypoechoic lesion after treatment; uT1, mucosal and submucosal disease; uT2, disease involving the hypoechoic muscularis propria; uT3, disease extension into the hyperechoic perirectal fat; and uT4, observation of the infiltration of adjacent organs. Clinical T response (downsizing) was defined as a reduction in the depth of tumor infiltration assessed by EUS before surgery compared with pretreatment uT stage. Four parameters were used to establish malignancy when assessing the lymph nodes (from more to less relevant); hypoechoic pattern $>$ sharply defined margins $>$ circular lymph nodes $>$ enlarged size over 10 mm. When all parameters were present, we considered the lymph node as positive (uN1). We also considered involved lymph nodes when 3 parameters were present but the size of the lymph node was between 5 and 10 mm. Oval lymph nodes with isoechoic patterns, well-defined margins, and size <5 mm were considered as negatives (uN0). Clinical N response was defined as an absence of previously detected lymph nodes assessed by EUS before surgery compared with pretreatment uN stage. Clinical stage response (downstaging) was also measured by comparison of initial uTN and post-CRT uTN. Tumor size modifications in circumference and surface were also calculated between pretreatment and posttreatment measures.

Standard pathological analysis was performed on all resection specimens according to the techniques described by Quirke et al.[11] Histological tumor stages (pTNM I–IV) and grades of differentiation (G1–G3) were determined according to guidelines established by the American Joint Committee on Cancer Cancer Staging Manual.[12] The tumor regression grade (TRG) was categorized by using the Memorial Sloan-Kettering Cancer Center system proposed by Ruo et al.[13] In this classification, a TRG based on a percentage of response is assigned by the pathologist as follows: TRG 0 is considered as the worst response with no evidence of treatment effect; TRG 1 as a response between 1% and 33%; TRG 2 as a response between 34% and 66%;

TABLE 1. Patient and tumor baseline characteristics

Variable	*n = 235 (%)*
Sex	
Male	106 (45)
Female	129 (55)
Distance to anal verge	
Lower (<7 cm)	136 (58)
Medium (7–11 cm)	65 (28)
Upper (>11 cm)	34 (14)
EUS initial stage	
Stage I (uT2 N0)	9 (4)
Stage II (uT3-T4 N0)	76 (32)
Stage III (T1-T4 N1 or N2)	150 (64)
Type of surgery	
LAR	177 (75)
APR	51 (22)
Hartmann procedure	7 (3)

EUS = endoscopic ultrasound; LAR = low anterior resection; APR = abdominoperineal resection.

TABLE 2. Histological findings and tumor regression grade

Variable	*n = 235 (%)*
Histological stage	
Stage 0 (pT0 N0)	31 (13)
Stage I (pT1-T2 N0)	73 (31)
Stage II (pT3-T4 N0)	57 (24)
Stage III (pT1-T4 N1 or N2)	74 (32)
Tumor regression grade (MSKCC)	
Grade 1	9 (4)
Grade 2	53 (23)
Grade 3	90 (38)
Grade 3+	52 (22)
Grade 4	31 (13)

MSKCC = Memorial Sloan-Kettering Cancer Center.

TRG 3 as a response between 67% and 95%; TRG 3+ as a response between 96% and 99%; and TRG 4 as a 100% response (complete pathological response with no viable tumor cells identified). Lymph nodes in the mesorectum were harvested by macroscopic dissection without using fat clearance techniques. The same experienced pathologist (J.S.) reviewed all pathological samples and assigned the TRG.

Statistics

A comparative analysis between post-CRT EUS staging and pTNM in the resected specimens was performed by raw percentage agreement to assess the accuracy of EUS to predict pathological stage. Accuracy of EUS to predict T stage and lymph node involvement was determined by assessment of sensitivity, specificity, and positive (PPV) and negative (NPV) predictive values. Qualitative variables are expressed as means of frequencies (percentages) and quantitative variables as medians (range). All statistical calculations were performed using SPSS software (version 17.0, SPSS Inc., Chicago, IL).

RESULTS

Within the 7-year study period, 235 patients with locally advanced rectal cancer underwent CRT followed by rectal resection at our institution. Demographics, patient baseline characteristics, tumor locations and sizes, and surgical procedures are presented in Table 1.

Clinical and Pathological Response

The median time interval between preoperative CRT and restaging by EUS was 41 days (range, 23–71 days). Time to surgery was classified into 3 groups; those patients treated at 36 days after finishing CRT or less (n = 25; 11%), from 36 to 42 days (n = 131; 56%), or more than 46 days (n = 79; 33%).

EUS imaging showed downsizing (uT response) in 54 patients (23%) and N-downstaging (uN response) in 110 patients (47%). A uTNM downstaging was documented in 129 patients (55%). We observed only one case of tumor progression between initial and posttreatment stage. Eighty-three patients (35%) achieved a nearly complete (TRG 3+) or complete (TRG 4) pathological response. Ninety patients (38%) showed moderate (TRG 3) and 62 patients (26%) showed poor pathological response (TRG 1–2). The median number of retrieved lymph nodes was 10 (range, 1–48). In relation to lymph node involvement, 160 patients (68%) were node negative (pN0) and 75 (32%) were node positive (pN+). Histological tumor stages (pTNM I–IV) and TRG categories are shown in Table 2. Thirty-one patients (13%) had a complete tumor response (TRG 4), and one patient showed complete tumor response in the bowel wall, but an affected lymph node in the mesorectum (pT0N1).

Accuracy of EUS

The correlation between post-CRT EUS findings and pathological results is shown in Tables 3 and 4. In assessing T stage, EUS was accurate in 126 (54%) patients. Overstaging occurred in 88 (37%) patients and was more commonly observed than understaging (21 patients; 9%). In the setting of lymph node involvement (pN), EUS was accurate in 175 (75%) patients. Accuracy of EUS in detecting nodal metastases achieved 39% of sensitivity and 91% of specificity. The PPV and NPV for N-staging were 67% and 76%. Despite this, 46 (19%) patients who were considered as uN0 after CRT showed affected lymph nodes in the surgical specimen. In Figure 1 we present the subset of patients from the study population who were uN0 at the initial diagnosis and continued to be uN0 after CRT. From a total of 83 patients with these features, 15 (18%) were misclassified by EUS and had affected lymph nodes in the pathology report. A separate comparative analysis (not shown in the article) did not identify any associated characteristics

TABLE 3. Comparison between EUS post-CRT and pathological T stage

EUS T stage	Pathology stage pT0	pT1	pT2	pT3	pT4	Total n	Understaged n (%)	Overstaged n (%)	Accuracy n (%)
uT0	**7**	2	6	0	0	15	8 (53)	0 (0)	47
uT1	2	**1**	1	0	0	4	1 (25)	2 (50)	25
uT2	6	5	**20**	8	0	39	8 (20)	11 (28)	51
uT3	14	7	44	**94**	4	163	4 (4)	65 (69)	58
uT4	0	0	4	6	**4**	14	0 (0)	10 (71)	28
Total	29	15	75	108	8	235	21 (9)	88 (37)	54

EUS = endoscopic ultrasound; CRT = chemoradiation.

with patients with false-positive and false-negative results. Finally, in assessing TN stage, EUS was more accurate for stage III disease than the rest of stages,as is presented in Table 5.

We also performed an additional analysis to identify potential clinical factors that may have influenced EUS accuracy. As presented in Table 6, accuracy was not modified by such factors as age, distance to anal verge, time to surgery, and the type of CRT. In assessing N stage in male patients compared with female patients, EUS accuracy showed statistical differences with a higher sensitivity (57% in males vs 30% in females; $P = .03$), but lower specificity (83% in males vs 94% in females; $P = .03$).

DISCUSSION

Our data indicate that, in our experience, the EUS has a limited role as a true predictor of clinical tumor response after preoperative CRT. Although EUS may allow a good prediction of involved lymph nodes in 75% of the study patients, there is still a lack of accuracy in nearly 1 in 5 patients (19%) who were understaged and showed affected lymph nodes in the surgical specimen.

A number of studies have been published on the utility of EUS in restaging rectal cancer after CRT that show varying ranges of accuracy rates from 38% to 75%.[14–21] Overstaging was more common in most series mainly because of radiation tissue changes such as tumor fibrosis or edema. As reported by Fleshman et al,[15] anterior rectal tumors may be challenging to restage after CRT because of fibrosis between the anterior perirectal fat and the prostatic capsule, which is an important interface to stage the tumor accurately. According to previous series, our study shows poor accuracy of EUS in assessing T stage after CRT. Fifty-four percent of the patients studied were staged correctly, and overstaging occurred in 37%. Accuracy increased to 58% in uT3 tumors where 94 of 163 patients were correctly staged and the percentage of understaged patients was low (4%). Of the 39 uT2 patients, we found that 8 (20%) were understaged and were shown to have pT3 tumors in the pathology report. Only 7 of 15 patients (50%) were correctly identified as having complete pathological response. We believe that a low EUS accuracy in assessing the T stage will not preclude a conservative approach for patients with uT0 to T2 and uN0 tumors after CRT. In those selected cases, a local excision of the scar could be performed by transanal endoscopic microsurgery to ensure the pathological stage or to plan radical surgery in case the tumor was understaged. This strategy, however, would only be valid if we would be able to achieve an accurate prediction of the nodal status.

The most critical factor in selecting the treatment modality for patients with rectal tumors after CRT depends on the nodal status (N stage). In this setting, the EUS reported accuracy for detection of involved lymph nodes ranges from 64% to 84%.[14–21] In our study, EUS correctly matched 75% of patients (175/235). Our data indicate that

TABLE 4. Comparison between EUS post-CRT and pathological N stage

EUS N stage	Pathology stage pN0	pN+	Total n	Understaged n (%)	Overstaged n (%)
uN0	**146**	46	160	46 (28)	0 (0)
uN+	14	**29**	43	0 (0)	14 (32)
Total	160	75	235	46 (19)	14 (6)

Sensitivity, 39%; specificity, 91%; PPV, 67%; NPV, 76%.
EUS = endoscopic ultrasound; CRT = chemoradiation; PPV = positive predictive value; NPV = negative predictive value.

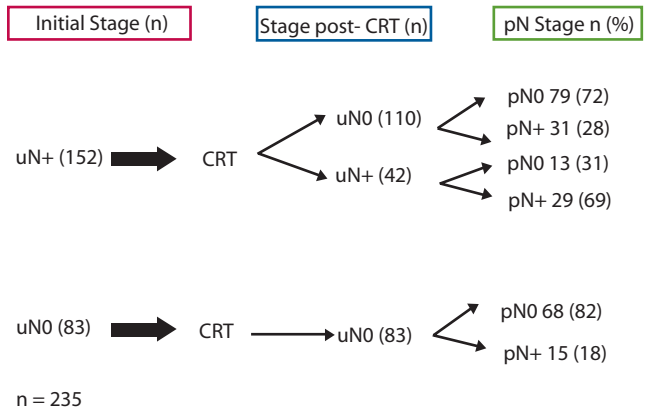

FIGURE 1. Lymph node status at diagnosis and after CRT correlated to pathological findings. CRT = chemoradiation.

TABLE 5. Comparison between EUS post-CRT and pathological TN stage

EUS TN stage	Pathology stage 0	I	II	III	Total n	Understaged n (%)	Overstaged n (%)	Accuracy n (%)
Stage 0	**7**	7	0	0	14	0 (0)	7 (50)	50
Stage I	8	**23**	4	8	43	8 (19)	12 (28)	53
Stage II	15	41	**42**	38	136	56 (41)	38 (28)	31
Stage III	1	2	11	**28**	42	14 (10)	0 (0)	67
Total	31	73	57	74	235	21 (9)	88 (37)	42

EUS = endoscopic ultrasound; CRT = chemoradiation.

even though we found a low sensitivity (39%) and PPV (67%), a relatively high specificity (91%) and NPV (72%) could be achieved. However, EUS still failed to detect lymph node involvement in the rest of the patients (46/160), which is, in our point of view, a relatively high percentage when considering planned use of EUS findings alone when planning a tailored surgical option after CRT. Furthermore, in the ideal candidates for a conservative approach, the uN0 patients at the diagnosis who are also uN0 after CRT, we consider that the 18% of missclassified patients too high for us to rely only on EUS findings to support a "wait and see" approach. In addition, one patient in our study showed a pathological complete response in the bowel wall with an affected lymph node in the mesorectum (pT0N1).

TABLE 6. Comparative analysis of potential clinical factors affecting EUS accuracy

Variable	uT-staging accuracy	uN-staging S/SP accuracy	uTN-staging accuracy
Global	54	S: 38 / SP: 91	42
Age			
<65 y	51	S: 41 / SP: 91	40
≥65 y	56	S: 31 / SP: 92	46
Sex			
Male	50	S: 57 / SP: 83	40
Female	49	S: 30 / SP: 94	47
Distance to anal verge			
<7 cm	49	S: 41 / SP: 91	44
7–11 cm	60	S: 33 / SP: 89	42
>11cm	51	S: 29 / SP: 96	36
Time to surgery			
<36 d	60	S: 20 / SP: 100	40
36–42 d	53	S: 41 / SP: 90	43
>42 d	49	S: 41 / SP: 90	41
Type of CRT			
Intensity-modulated RT (n = 153)	50	S: 35 / SP: 91	40
External-beam RT (n = 82)	48	S: 32 / SP: 93	49

All values shown are percentages. None of the comparisons between percentages observed (from different categories of the same variable vs global) were statistically significant (χ^2 for difference of proportions), with the exception of sex. In male patients, EUS showed higher sensitivity (57% males vs 30% females; $P = .03$) but lower specificity (83% males vs females 94%; $P = .03$).
EUS = endoscopic ultrasound; RT = radiation; S = sensibility; SP = specificity.

We believe that our variations in accuracy with other series may be related to different criteria for nodal positivity. Currently, nodal size is the most frequent and reliable criterion for defining metastasic lymph nodes, but there is no consensus on the cutoff measure. Using a cutoff of 1 cm, we overstaged 32% of patients (14/43) who were uN+ after CRT and pN0. Other series, such as the one published by Vanagunas et al,[18] noted similar overall accuracy rates in N staging with the 1-cm rule, whereas others recommended that any lymph node greater than 5 mm should be considered to be malignant. Pomerri et al,[22] comparing both criteria in 53 patients who underwent MRI, CT scan, and EUS after CRT, found that using the 10-mm cutoff instead the 5-mm cutoff gave rise to overall accuracy and may be the best node size cutoff for predicting nodal involvement after CRT. In contrast, the Brazilian group of Habr-Gama found in a subset of 31 pT0-T2 patients after TME that 95% of all lymph nodes were <5 mm and 50% of the involved lymph nodes were <3 mm.[23] They concluded that individual lymph node size is not a good predictor of nodal metastases. All these discrepancies in the literature show that the current criteria available for predicting lymph node involvement remain a matter of debate. Therefore, we considered in our group that a combination of suspicious morphologic lymph node characteristics might be more important than the size itself when deciding whether a lymph node is involved or not. In addition, we have performed an analysis to identify any potential factor that may have an influence in accuracy. We have found a significant association between sex and accuracy, because EUS showed more sensitivity in male patients; however, we believe that these differences are too small to be clinically relevant.

Our study has a number of limitations that deserve mention. Unlike other recent studies, we did not perform any other imaging modality such as a CT or MRI to be compared with our EUS findings. Consequently, we do not have a control with which to compare our accuracy; however, we tried to eliminate the interobserver limitations by having the same physician perform all the EUS. Second, we did not use some EUS applications such the 3D view or the Doppler findings that may be useful in assessing tumor's response.[24] Finally, our data were derived

from consecutive patients treated at a relatively small colorectal unit, and the sample size, although large compared with previously published series, was relatively small.

CONCLUSIONS

The radiological inability to truly diagnose tumor response before removal of the rectum is still the most significant limitation to the use of CRT as the only form of therapy for patients with rectal cancer. As a result, there is a disagreement among the surgeons on issues regarding a more conservative approach ("wait and see" or local excision alone) for patients with a major clinical response after CRT. Our data showed that, although we made an effort to reduce any bias related to the time elapsed between completing CRT and surgery and the interobserver variability, we did not achieve the expected accuracy rates to rely exclusively on EUS findings to support a "wait and see" approach after CRT. Based on this, we believe that further examinations such an MRI should be performed in an effort to determine more accurately the tumor stage before attempting any conservative surgical approach.

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