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ORIGINAL RESEARCH ARTICLE

Endoscopic ultrasound as a predictor of pathologic complete response in rectal cancer

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ABSTRACT

The possibility of preoperative prediction of pathologic complete response in rectal cancer has been studied in order to identify patients who would respond to neoadjuvant therapy and to individualize therapeutic strategies. Endoscopic ultrasound of the rectum is an accurate method for the evaluation of local tumor and lymph node invasion. **Objective:** To evaluate the potential of endoscopic ultrasound as a predictor of complete pathological response to neoadjuvant treatment in patients with locally advanced rectal cancer. **Material and methods:** Retrospective study of patients with rectal cancer from January 2014 to December 2016. **Results:** We obtained a statistical association between T stage by endoscopic ultrasound and complete pathological response ($p = 0.015$). It is not so for N, sphincter involvement, circumferential involvement and maximum tumor thickness ($p = 0.723$, $p = 0.510$, $p = 0.233$ and $p = 0.114$, respectively). When multivariate logistic regression analysis was applied to assess the degree of influence of the predictor variables on pathologic response, none of these variables was associated with complete pathologic response. **Conclusion:** Prediction of pathologic complete response in rectal cancer has been considered as the crucial point upon which treatments for rectal cancer could be individualized. So far, no imaging method has been able to demonstrate efficacy in predicting complete pathologic response, and in turn there is no direct association between any endosonographic finding that can accurately predict it.

Keywords: Pathologic Complete Response; Rectal Cancer; Endoscopic Ultrasound

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1. Introduction

The therapy of choice for locally advanced non-metastatic rectal cancer (American Joint Committee on Cancer stage II/III) consists of multimodality therapy based on preoperative chemo-radiotherapy (CRT), total mesorectal excision (TEM), and adjuvant chemotherapy[1-3].

Pathologic complete response (PRc) to neoadjuvant CRT has been associated with reduced distant disease, improved local control, local recurrences of less than 1%, and survival of more than 95% at 5 years compared to patients without PRc[4,5].

The possibility of preoperative prediction of PRc by clinical, pathological, radiological and molecular methods has been studied[6-9]. In order to identify patients who would respond to neoadjuvant therapy, we made special therapeutic strategies to avoid radical surgeries and definitive stomas, preserving the rectum without compromising the oncologic results of the patients[4,10].

Results from three groups have found an association between clinical T stage (TNM staging system) and the likelihood of obtaining

PRc of 58% for T1, 28% for T2, 16% for T3 and 12% for T4.8. In turn, PRc has been associated with good tumor differentiation, small tumor diameter, early stage of T and N, non-circumferential and non-ulcerated tumors, and low pretreatment carcinoembryonic antigen (CEA) levels[6,11,12]. However, these have low sensitivity and specificity and other studies contradict these results[6].

Endoscopic ultrasound (EUS) of the rectum is one of the most accurate methods for the evaluation of local invasion of rectal cancer and peri-rectal lymph nodes[13]. Comparative studies show that the accuracy of EUS for T staging is 80–95% (**Figure 1**) compared to computed tomography (CT) (65–75%) and MRI (75–85%).

For lymph node staging it is 70–75% (**Figure 2**) compared to CT (55–65%) and MRI (60–70%)[14]. EUS is recommended as an accurate staging method for the selection of early lesions suitable for endoscopic resection or transanal resection[13].

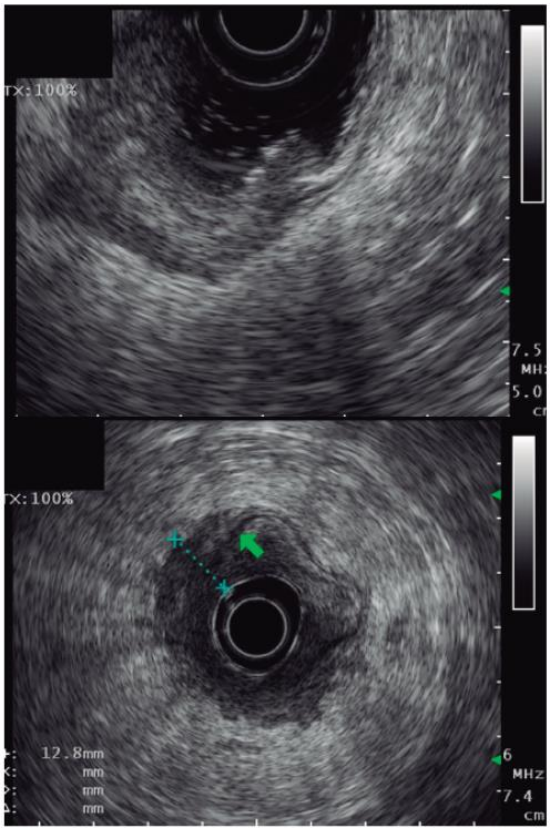

Figure 1. Endoscopic ultrasound evaluation of the primary tumor (T) according to TNM in rectal cancer. The tumor invades through the muscularis propria into the peri-colorectal tissue (T3).

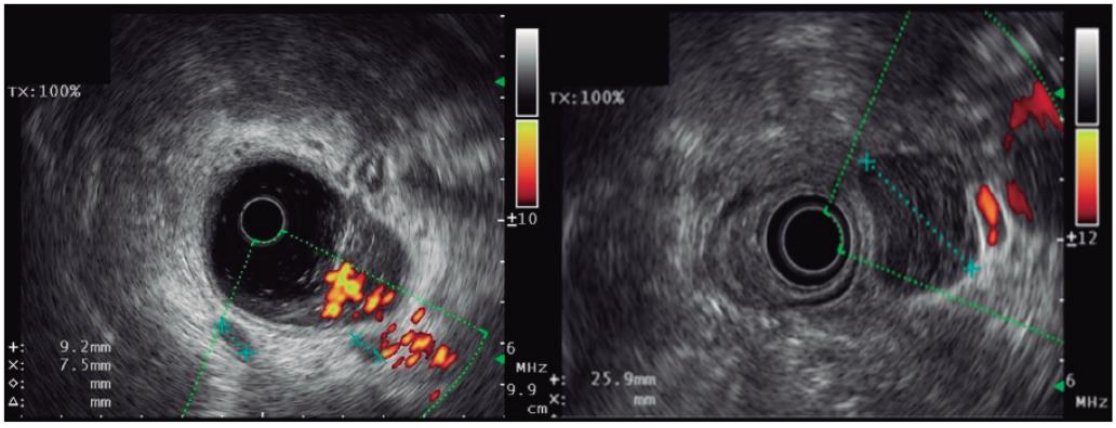

Figure 2. Endoscopic ultrasound assessment of regional adenopathies in rectal tumors.

The accuracy of staging after neoadjuvant radiotherapy decreases significantly due to edema, necrosis and fibrosis caused by radiotherapy, which is why the diagnostic accuracy of EUS for T decreases to 50% in the post-radiotherapy setting[15,16]. No imaging study has been shown to be the most accurate for restaging after preoperative therapy and before surgery[17].

However, the use of EUS as a predictor of PRc has not been widely evaluated. The study by Li *et al.* is the first to propose serial measurements of EUS and post-CRT tumor thickness as predictors of PRc, and in turn improve the survival[18].

2. Target

This study aims to evaluate the potential of endoscopic ultrasound as a predictor of pathologic complete response to neoadjuvant treatment after surgery in patients with locally advanced rectal cancer.

3. Material and methods

A retrospective study of patients with rectal cancer registered during the period from January 2014 to December 2016 at the National Cancer Institute of Mexico was performed, obtaining approval of the Ethics Committee of the Institute.

3.1 Inclusion criteria

Patients with locally advanced rectal cancer (American Joint Committee on Cancer stage II/III) confirmed by physical examination, chest X-ray, or CT, without previous treatment were included. Those patients who underwent colonoscopy with histopathologic confirmation of adenocarcinoma, have tumor located below the sigmoid-straight junction or in the first 15 cm from the pectineal line.

Rectal endoscopic ultrasonography was used for staging before treatment, neoadjuvant RK, TME surgical resection, and pathological staging after treatment.

3.2 Exclusion criteria

Patients excluded were those with stenosing tumors not frankable by colonoscopy or endoscopic ultrasound, with unresectable or synchronous tumors.

The pre-treatment stage was determined by endoscopic ultrasound using an Olympus GF-UE160 radial echoendoscope with frequencies of 7.5–12 MHz, with the patient in left lateral decubitus the tracing was performed from the bifurcation of the aorta to the identification of the anal sphincters. The following variables were described: maximum tumor thickness (>10 and ≤10 mm), sphincter involvement, circumferential tumor involvement (>50% and ≤50%) and clinical stage by EUS according to the AJCC TNM classification 7th edition.

Patient demographic, clinical and pathologic data were collected, such as age, gender, pretreatment carcinoembryonic antigen (CEA) measurement, with a cutoff value >10 and ≤10 ng/ml. Neoadjuvant treatment was a long scheme of intensity-modulated radiotherapy plus concomitant chemotherapy.

The analysis of the pathological specimens was performed by the Pathology Service and was taken from the electronic file. The quality of mesorectal excision, the degree of surgical resection of the tumor, the pathologic stage (ypTNM) and the degree of pathologic response were evaluated.

According to the AJCC 2010 tumor regression grade (TRG) (modified Ryan classification), the latter being classified into: TRG0, complete response (no viable tumor cells); TRG1, moderate response (small group of tumor cells or single cells); TRG2, minimal response (residual cancer with fibrosis) and TRG3, poor response (with minimal or no tumor cell elimination).

In turn, for the purpose of this study, the pathological response was classified into the group with PRc (TRG0) and all others without response or with variable response as the group without complete pathological response (TRG1, TRG2, TRG3)[19].

For this study, sphincter involvement was considered when the tumor infiltrates one or both sphincters of the rectum; circumferential involvement of the tumor, when there is circumferential involvement if the tumor is distributed in more than 50% of the circumference of the rectum; tumor thickness, when at the maximum measurement in millimeters of rectal wall thickness at the tumor site; grade of surgical resection, when defined as R1 if the circumferential resection margin is positive for neoplasia, or if the resection margin is less than 1 mm and R0 if the circumferential resection margin is negative for neoplasia[4]; pathologic complete response (PRc), when there is no adenocarcinoma cells in the wall of the rectum or in regional lymph nodes (ypT0N0M0), classified as TRG0[4,20]; no complete pathologic response, when there is absence of complete pathologic response or variable degree of response (TRG1, TRG2, TRG3).

3.3 Statistical analysis

The possible differences between patients who had PRc versus those who did not have PRc in clinicopathologic variables were evaluated with the chi-square test. Logistic regression analysis was performed for the prediction of PRc. The Stata/MP 13.0 program (Stata, College Station, TX) was used for statistical analysis, with p values <0.05 being

considered significant.

Differences between groups were evaluated with the chi-square test. Logistic regression analysis was performed for prediction of the dependent variable. A p value <0.05 was considered statistically significant. Stata/MP 13.0 (Stata, College Station, TX) was used for statistical analysis.

4. Results

Seventy-eight patients were included, all of whom met the established inclusion criteria. All underwent rectal EUS, received neoadjuvant CRT, surgical resection plus MTE, and postoperative pathologic staging.

Included patients received intensity-modulated radiotherapy at a dose of 50.4 Gy in 28 fractions. The concomitant chemotherapy regimen used was capecitabine 2.5g⁄m^2 day 1–14 every 3 weeks for 4 cycles in 87.2% of patients, and capecitabine plus oxaliplatin in 12.8%.

The demographic characteristics of the patients and the variables associated with PRc are shown in **Table 1**.

Women (n = 32) corresponded to 41.0%, and 59.0% (n = 46) to men, with a median age of 60.5 (range: 32–83). Pre-treatment CEA with a median of 3.28 ng/ml (range: 0.39–3,321). The clinical stages obtained according to endoscopic ultrasound were stages I to IIIC. For endosonographic findings regarding tumor assessment of the rectal wall, 10.3% (n = 8) corresponded to T2, 65.4% to T3 (n = 51), and 24.4% to T4 (n = 19). For lymphatic staging, 33.3% (n = 26) corresponded to N0, and with the presence of lymph nodes in 66.7% (n = 52). Sphincter involvement in 30.7% (n = 24), circumferential involvement of the rectum by the tumor in >50% of the lumen in 67.9% of cases (n = 53). With respect to the measurement of the maximum tumor thickness, this was assessed in 56 of the 78 patients. The median maximum tumor thickness was 15.7 mm (range: 8–34.6), for which a cut-off of >10 mm and ≤10 mm was established according to the distribution of the data. Histopathological results after neoadjuvant and surgery (**Table 2**) were established as T0 16.7% (n = 13), Tis 2.6% (n = 2), T1 10.2% (n = 8), T2 30.7% (n = 24), T3 33% (n = 26) and T4 6.4% (n = 5). For this pathological

Table 1. Baseline patient characteristics and variables associated with PRc (n = 78)

Feature	**n (%)**
Age (years) median (range)	60.5 (32–83)
Genre	
Women n (%)	32 (41)
Men n (%)	46 (59)
Pretreatment CEA (ng/ml) median (range)	3.28 (0.39–3.321)
Clinical stage by EUS	
I	2 (2.6)
IIA	18 (23.1)
IIB	4 (5.1)
IIC	2 (2.6)
IIIA	5 (6.4)
IIIB	32 (41.0)
IIIC	15 (19.2)
Clinical stage of T by EUS	
T2	8 (10.3)
T3	51 (65.4)
T4	19 (24.4)
Clinical stage of N by EUS	
NO	26 (33.3)
N1A	15(19.2)
N1B	20 (25.6)
N1C	1 (1.3)
N2A	9 (11.5)
N2B	7 (9.0)
Sphincter involvement	
Yes	24 (30.8)
No	54 (69.2)
Circumferential involvement	
>50%	53 (67.9)
≤50%	25 (32.1)
Tumor thickness (mm) median (range)	15.7 (8–34.6)

Table 2. Post-treaTEMnt histopathologic findings (n = 78)

Variable	n(%)
Typ	
T0	13 (16.7)
Tis	2 (2.6)
T1	8 (10.2)
T2	24 (30.8)
T3	26 (33.3)
T4	5 (6.4)
ypN	
NO	55 (70.5)
N1A	8 (10.2)
N1B	6 (7.7)
N1C	3 (3.8)
N2A	3 (3.8)
N2B	3 (3.8)
Grade of tumor resection	
R0	72 (92.3)
R1	6(7.7)
Total excision of the mesorectum	
Complete	63 (80.8)
Not complete	15 (19.2)
Tumor regression grade (AJCC)	
0 (Complete)	13 (16.6)
1 (Moderate)	24 (30.8)
2 (Minimum)	24 (30.8)
3 (Poor)	17 (21.8)
Clustered pathological response	
Complete	13 (16.7)
No PRc	65 (83.3)

Note: AJCC: American Joint Committee on Cancer; PRc: pathologic complete response.

diagnosis of lymph nodes, N0 70.5% (n = 55), and grouping all stages with the presence of positive adenopathies for malignancy 29.5% (n = 23).

For the R0 resection grade, the rate was 92.3% (n = 72) and R1 was 7.7% (n = 6). In 80.8% (n = 63) MTE was performed, and in 19.2% (n = 15) the excision of the mesorectum was incomplete. Finally, the PRc (TRG0) obtained was 16.7% (n = 13), and when moderate, minimal and no response (TRG1, TRG2 and TRG3) were grouped together, the rate was 83.3% (n = 65). Within the group of patients with PRc, 30.7% corresponded to T2 (n = 4), 38.5% to T3 (n = 5) and 30.7% to T4 (n = 4). For the group without PRc, we found that the T2 stage was 6.1% (n = 4), T3 70.8% (n = 46) and T4 23.1% (n = 15).

Table 3. Predictors of PR following neoadjuvant CRT and surgery (n = 78)

Variables	PRc n	No PRc n	*p*
Gender			
Male	8	39	0.837
Female	5	27	
Age (years)			
>45	10	55	0.497
≤45	3	10	
CEA pretreatment (ng/ml)			
>10	2	15	0.540
<10	11	50	
T for EUS			
T2	4	4	0.015*
T3	5	46	
T4	4	15	
N for EUS			
N0	6	20	0.723
N1a	2	13	
N1b	4	16	
N1c	0	1	
N2a	1	8	
N2b	0	7	
Sphincter involvement			
Yes	3	21	0.510
No	10	44	
Circumferential involvement			
>50%	7	46	0.233
≤50%	6	19	
Tumor thickness (mm)			
>10	8	38	0.114
<10	4	6	

Note: PRc: complete pathologic response; CEA: carcinoembryonic antigen; EUS: endoscopic ultrasound; CRT: chemo-radiotherapy; CEA: carcinoembryonic antigen. Chi^2 * $p < 0.05$.

In accordance with the objective of the study, which is to evaluate the potential of endoscopic ultrasound as a predictor of CPR, when analyzing the factors that we determined as possible predictors by means of the chi-square test, we obtained a statistical association between the stage of T for EUS and CPR (p = 0.015). It is not so for N by EUS, sphincter involvement, circumferential involvement and maximum tumor thickness (p = 0.723, p = 0.510, p = 0.233 and p = 0.114 respectively) (**Table 3**).

In turn, when multivariate logistic regression analysis was applied to assess the degree of influence of the predictor variables on the pathological response, none of these variables was associated with the PRc (**Table 4**).

Table 4. Multivariate predictors of PRc

Variables	***p****
Generate	0.541
Age	0.362
CEA	0.426
T2	0.895
T3	0.393
Sphincter	0.539
Circumference	0.147
Thickness	0.159

Note: PRc: Pathologic complete response; CEA: Carcinoembryonic antigen. *Logistic regression analysis.

5. Discussion

In our study we documented a pathologic complete response rate of 16.7%, which is in agreement with literature reports of 10 to 20%[4,6,21]. In the univariate statistical analysis, we found an association between T stage by EUS with PRc, not so with the other probable predictors (sphincter involvement, circumferential tumor involvement, tumor thickness). However, in the logistic regression analysis no *p* value obtained was statistically significant. Therefore, we can say that there is no direct relationship between any endoscopic ultrasound measurement in the pre-treatment period with the prediction of PRc, and the identification of patients who would obtain a PRc before treatment cannot be conclusively established.

In the study by Ning *et al.*, they performed sequential endoscopic ultrasound measurements of the largest tumor diameter in 41 patients with stage II and III rectal cancer, prior to the start of neoadjuvant treatment, 2 weeks after its initiation, and 6 to 8 weeks after the end of chemo-radiotherapy. They found a correlation between the post-treatment maximum thickness measurement and the radius measurement after neoadjuvant CRT with the pre-treatment diameter, with the PRc and the degree of tumor regression (p = 0.001 and p = 0.026 re-

spectively).

Although previous studies have suggested that the accuracy and usefulness of EUS in the restaging of rectal cancer is compromised by the edema and fibrosis that neoadjuvant treatment causes, these results suggest that the correlation of post-treatment and pre-treatment endoscopic ultrasound measurement, in addition to the maximum tumor thickness measurement in the post-neoadjuvant period could predict the therapeutic sensitivity of rectal cancer[18]. It is worth mentioning that in addition to the sample size, the fact of having only one pre-treatment measurement may affect the results obtained in our study.

Different factors influence the pathologic response to neoadjuvant therapy, from the different sensitivity to chemo-radiotherapy due to the individual nature of the tumor, the time between the end of neoadjuvant therapy to surgical resection, among others[9,22,23].

Multiple uncontrolled prospective studies report that the local recurrence rate and overall survival in patients with PRc who underwent surgical procedures without MTE is similar to those who underwent MTE[10,24].

Given the good oncologic outcomes of patients with complete pathologic response, efforts to identify this group have become a challenge.

The major obstacle is that such response can only be assessed with the surgical specimen. Clinical prediction of pathologic response would allow a selection of patients in whom surgery and MTE could be avoided[3,25].

6. Conclusion

The prediction of pathologic complete response in locally advanced rectal cancer is a challenge that continues to be investigated, since this topic has been considered as the crucial point on which treatments for locally advanced rectal cancer could be personalized. So far, no imaging method has been able to demonstrate efficacy in predicting complete pathologic response, and there is no direct association between any endosonographic finding that can accurately predict it[21].

The variable responses among tumors to neoadjuvant chemo-radiotherapy suggest a complex relationship with tumor biology, probably due to diverse molecular pathways that regulate sensitivity to chemo-radiotherapy[6].

Conflict of interest

The authors declare that they have no conflicts of interest.

Abbreviations

CRT: Chemo-radiotherapy.
TEM: Total excision of the mesorectum.
PRc: Complete pathological response.
CEA: Carcinoembryonic antigen.
EUS: Endoscopic ultrasound.
CT: Computed tomography.

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