Original Article

Utility of Rectoscopy in the Assessment of Response to Neoadjuvant Treatment for Locally Advanced Rectal Cancer

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ABSTRACT

Background/Aims: The management of locally advanced rectal cancer has changed substantially over the last few decades with neoadjuvant chemoradiotherapy. The aim of the present study is to compare the results between neoadjuvant post-treatment rectoscopy and the anatomopathological findings of the surgical specimen. **Patients and Methods:** We conducted a prospective study of 67 patients with locally advanced adenocarcinoma of the rectum (stages II and III). Two groups were established: One with complete clinical response (cCR) and one without (non-cCR), based on the findings at rectoscopy. Assessment of tumor regression grade in the surgical specimen was determined using Mandard's tumor regression scale. **Results:** Seventeen patients showed a cCR. Thirty-five biopsies were negative and 32 were positive for mailgnancy. All the cCR patients had a negative biopsy ($P < 0.0001$). All 32 positive biopsies revealed the presence of adenocarcinoma, and of the 35 negative biopsies, 18 had no malignancy and 17 were diagnosed with adenocarcinoma ($P < 0.0001$). Sixteen of the 17 cCR patients showed a complete pathological response and one patient showed the presence of adenocarcinoma. Of the 50 non-cCR patients 48 revealed the presence of adenocarcinoma and two had absence of malignancy. According to the Mandard classification, 16 of the 17 cCR patients were grade I and 1 grade II; 2 non-cCR patients were grade I, 7 grade II, 13 grade III, 19 grade IV, and 9 grade V. **Conclusions:** Endoscopic and histological findings could be determinants in the assessment of response to neoadjuvant treatment.

Key Words: Complete clinical response, neoadjuvant chemoradiation, rectal cancer, rectoscopy

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Rectal carcinoma is a neoplasm of great relevance in everyday clinical practice.[1] Neoadjuvant chemoradiation therapy (CRT) is currently considered fundamental in the treatment for locally advanced rectal cancer, due mainly to the reduced risk of local recurrence and to the rates of sphincter conservation.[2,3]

Various studies have reported the occurrence of complete tumor regression determined by the absence of residual cancer cells in the specimen after a radical rectal resection with total mesorectal excision.[4] This phenomenon is known as pathological complete response (pCR). It has better long-term outcomes and a very low or zero rate of both local recurrences and distant relapses.[5,6] However, such an outcome requires radical surgery that is not without significant morbidity and mortality for the patient. Given the good prognosis of patients with pCR, new and more conservative treatment strategies are being developed such as local resection or the "wait and see" approach.[7,8]

Neoadjuvant CRT could identify a select group of patients in whom radical surgery might be avoided. To allow selection of such patients, tumor response must be assessed once CRT is completed. The complementary tests for re-staging (digital examination, endorectal ultrasound, rectal rectoscopy, nuclear magnetic resonance [NMR] and Positron emission

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tomography [PET]-CT) are exploratory techniques considered controversial and inaccurate.[9-13] Rectoscopy allows direct visualization of the response to treatment and the possibility of taking biopsies from the tumor bed.[14]

The aim of this study is to compare the results between neoadjuvant post-treatment rectoscopy (via visual response and biopsy) and the anatomopathological findings of the surgical specimen.

PATIENTS AND METHODS

Study design and patients

Between May 2012 and February 2015, a prospective longitudinal study was conducted in patients with distal rectal cancer. Inclusion criteria included patients with locally advanced adenocarcinoma of the rectum (stages II and III) treated with neoadjuvant CRT and primary rectal cancer with the inferior border located no more than 12 cm from the anal verge. The study protocol was approved by the ethical committee of the Virgen de la Arrixaca Clinical University Hospital (Murcia), a tertiary referral hospital. All the patients were informed of the objective of the study in their native language, and their participation was voluntary once they had signed their informed consent.

All the patients followed the conventional procedure for diagnosis and staging to characterize the rectal lesion using the standard techniques of digital rectal exam, endorectal ultrasound, complete rectal rectoscopy with biopsy, and NMR of the pelvis. Moreover, staging of the distant disease was established by thoracic–abdominal–pelvic CT and PET-CT where necessary.

All the patients received the protocol established by our hospital based on a long-course radiation therapy (RT) with a total dose of 45 Gy and chemotherapy with 5-fluorouracil for the time the RT treatment lasted.[15]

Endoscopic protocol

Two examinations were done in all the patients using flexible rectoscopy: One for initial diagnosis and one 8 weeks after completion of the neoadjuvant treatment to assess response. The same colorectal surgeon and the same endoscopist performed assessments on every single patient at baseline and after CRT. During the rectoscopy, four biopsy specimens were taken in the tumor region. All the patients underwent an anterior resection or an abdominoperineal amputation in an interval of 2 weeks (range: 1–4) from the time of re-assessment colonoscopy.

The criteria for establishing a complete clinical response (cCR) were disappearance of the lesion, whitening of the mucosa in an area of the rectal wall, presence of telangiectasias, loss of flexibility/pliability of the rectal wall harboring the scar and when the lesion could not be seen[14] [Figure 1].

Findings suggestive of a noncomplete clinical response (non-cCR) were defined by any residual deep ulceration with or without a necrotic center, any superficial ulcer or irregularity (even in the presence of only mucosal ulceration), nodularity and any significant stenosis impeding the rectoscopy from sliding through even in the presence of mucosal complete integrity[14] [Figure 2].

Pathological examination

The post-neoadjuvancy histopathological response was assessed on the basis of the anatomopathological report of the biopsy obtained during post-treatment rectal rectoscopy and was considered positive when there were signs suggesting malignancy and negative when there was no malignancy.

The surgical specimen was analyzed by the same pathologist. Assessment of tumor regression grade in the surgical specimen was determined at all times using the following classifications:

- Mandard tumor regression scale:[16,17] Grade I, absence of neoplastic cells (100% response); Grade II, isolated tumor cells (90%); Grade III, neoplastic cells but fibrosis still predominates (50%–89%); Grade IV, predominance of neoplastic cells (10%–49%); Grade V, absence of regressive changes (<10%).

Grade I was classed as a pCR and grades II, III, IV, and V as an incomplete pathological response.

Statistical analysis

In the statistical analysis of the data, the numerical variables are expressed as mean ± standard deviation and the qualitative variables as frequencies and percentages. For the comparative study of means we use the nonparametric test (Kruskal–Wallis). The Chi-squared test is used to contrast the qualitative variables. All the results are considered statistically significant for $P \leq 0.05$. The statistical analysis was done with the SPSS software (v19.0; IBM Corporation, Armonk, NY, USA).

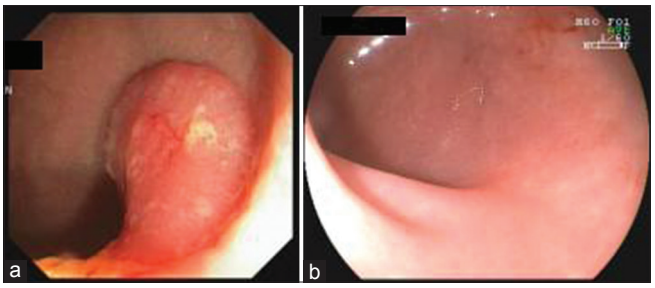

Figure 1: Patient with a complete clinical response (Figure 1a: Pre-treatment; Figure 1b: Post-treatment)

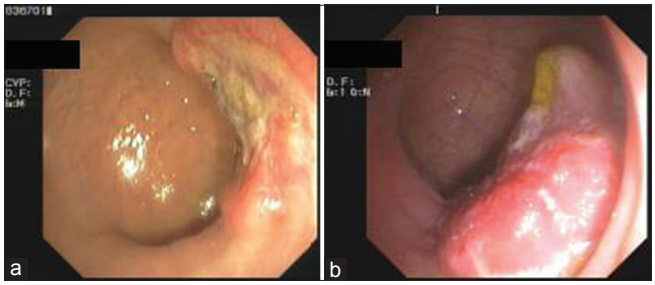

Figure 2: Patient with incomplete clinical response (Figure 2a: Pre-treatment; Figure 2b: Post-treatment)

RESULTS

A total of 75 patients underwent neoadjuvant CRT. In total, eight patients were excluded from further analysis (4 did not go for surgery, two had anal excision, and two had inadequate data). The remaining 67 patients who underwent the surgery incorporating total mesorectal excision were included in the final analysis. The clinical characteristics of the patients are listed in Table 1.

Seventeen of the 67 patients showed a cCR and 50 a non-cCR. Thirty-five biopsies were negative and 32 were positive for malignancy. All the cCR patients had a negative biopsy.

The results comparing endoscopic response to biopsy result and pathological anatomy of the specimen are shown in Table 2. On comparing endoscopic response and biopsy result we found that all 17 patients with a cCR had a negative biopsy for malignancy, whereas 32 of the 50 with a non-cCR had a positive biopsy and 18 had a negative biopsy, with statistically significant differences ($P < 0.0001$). The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were 100% (IC95%: 100%–100%), 49% (IC95%: 32%–65%), 64% (IC95%: 51%–77%), 100% (IC95%: 100%–100%), respectively.

When endoscopic response and pathological anatomy of the specimen were compared, 16 of the 17 patients with a cCR showed a pCR and one had the presence of adenocarcinoma. Of the 50 patients with a non-cCR, 48 showed the presence of adenocarcinoma, whereas two had absence of malignancy, with statistically significant differences ($P < 0.0001$). The sensitivity, specificity, PPV, and NPV were 98% (IC95%: 94%–102%), 89% (IC95%: 74%–103%), 95.6% (IC95%: 91%–101%), and 94% (IC95%: 83%–105%), respectively.

When biopsy result and pathological anatomy of the specimen were compared, all 32 positive biopsies were found to have the presence of adenocarcinoma. Of the 35 negative biopsies, 18 had absence of malignancy and 17 adenocarcinoma, with statistically significant differences ($P < 0.0001$). The sensitivity, specificity, PPV, and NPV were 65% (IC95%:527%–79%), 100% (IC95%: 100%–100%), 100% (IC95%: 100%–100%), and 51% (IC95%: 35%–68%), respectively.

Table 1: Demographic details of the patients

Age, years (range)	66.05 (34-88)
Gender	29 female and 38 male
Distance from the anal verge, cm	4 (1-12)
Pre-CRT CEA (ng/mL)	3 (0.8-100)
Pre-CRT tumor staging	
T2N1	7
T3N0	19
T3N1	17
T3N2	15
T4N0	3
T4N1	1
T4N2	5
Pathology staging	
ypT0N0	16
ypT1N1	1
ypT1N0	3
ypT2N0	14
ypT2N1	2
ypT3N0	12
ypT3N1	12
ypT3N2	4
ypT4N0	1
ypT4N1	2

Table 2: Comparison of endoscopic response with biopsy result and pathological anatomy of the specimen

	Biopsy result		Pathological anatomy	
	Positive (*N*=32)	Negative (*N*=35)	Adenocarcinoma (*N*=49)	Normal (*N*=18)
Complete clinical response (*N*=17)	0	17	1	16
Incomplete clinical response (*N*=50)	32	18	48	2

When endoscopic response and tumor regression grade were compared according to the Mandard classification, 16 of the 17 patients with a cCR had grade I and one grade II. Of the 50 patients with a non-cCR 2 were grade I, 7 grade II, 13 grade III, 19 grade IV, and 9 grade V.

The same patient with presence of adenocarcinoma in the pathological anatomy of the specimen of the 17 patients with cCR and negative biopsy results, presented tumor nodal involvement in the surgical specimen (N1).

DISCUSSION

Among the advances made in the treatment of rectal cancer, the use of neoadjuvant CRT has led to a change in the

management of this disease. We are currently faced with new challenges based on achieving a complete or partial response to neoadjuvant treatment. The use of rectoscopy might prove an important tool for re-assessing patients once the neoadjuvant treatment is finished, but its role in the management of this type of patient and its utility for establishing other less invasive treatment options have not been established in everyday clinical practice even though they have been standardized.[14]

Post-CRT rectoscopy offers the possibility of direct tumor visualization and also enables us to obtain a histopathological sample, which means it might contribute to establishing patient selection criteria that allow less invasive surgical resections and even the possibility of the "wait and see" protocol to prevent unnecessary surgery and consequent adverse events.

The literature is scarce and controversial regarding the utility of re-assessment rectoscopy after neoadjuvant CRT for locally rectal advanced cancer. Some authors[18-20] show a poor correlation between cCR and pCR. These studies have the disadvantage of being retrospective, of having very low rates of intercorrelation, of being conducted by different surgeons (with the interobserver differences that this involves), of using currently obsolete CRT regimens and of performing rectoscopy 4–6 weeks after CRT completion. More recently, another retrospective study with similar limitations recommends that re-biopsy should be performed in all patients.[21]

Rectoscopy in these patients must always be performed by the same endoscopist backed up by a well-experienced colorectal surgeon. Subjectivity toward the findings decreases if the test is always done by the same professional guided by the same criteria described previously for assessing tumor response. Response to neoadjuvant treatment is not uniform and is related to the time interval after CRT completion, tumor or patient characteristics, and tumor biology. As for the time necessary between the completion of the neoadjuvant treatment and the endoscopic re-assessment of the tumor response, various retrospective studies have agreed on an interval of 7–8 weeks to achieve a cCR complete response, as re-assessing the patient before this time may lead to underdiagnosis of the response to neoadjuvant treatment in patients that could well develop further tumor regression. In the present study, the interval is set at the 8th week after CRT.[22,23]

One of the aspects generating most controversy is the utility of biopsies in assessing the response to treatment. On the one hand, the biopsy confirmed absence of malignancy in all the cases in which a cCR was obtained. However, when we had a non-cCR the biopsy was negative in 36%. This problem is also reflected when biopsy data are compared with the pathological anatomy of the surgical specimen: Obviously the presence of adenocarcinoma was confirmed in all the positive biopsies, but the presence of adenocarcinoma was also shown in 48% of the negative biopsies. This result is probably because the biopsy only corresponds to a portion of the tumor. It can be said therefore that biopsies are not useful in cases of non-cCR, as decision making is hampered by their high percentage of false negatives. Conversely, a negative biopsy in patients with endoscopic criteria of a cCR due to the high sensitivity and 100% negative predictive value shown by the test, takes on a relevant role for these patients, and might help us in the difficult process of decision making.

There is clearly a close relationship between rectoscopy findings and tumor response grade. As reported in other studies publications, when the rectoscopy strictly fulfils the criteria of a cCR and a negative biopsy is obtained, we can predict the probability of encountering a pCR.[24-26] Suzuki *et al*. demonstrated that morphological changes on rectoscopy were significantly related to the degree of tumor shrinkage, but they only had a 2% pCR and failed to establish a statistically significant relationship between cCR and pCR. García-Aguilar *et al*.[27] present similar data among patients with cT2N0 undergoing CRT where >90% cCR corresponded to ypT0 after local excision. Smith *et al*.[28,29] published a study in which they compared photographs to final pathology. In this study they found that the criteria for cCR had NPV and PPV ≥ 90%, similar to the present study. Even though not all patients with pCR were detected with clinical assessment, those with cCR were correct in more than 90% of the cases. In the present study, all the patients with a cCR and negative biopsy finally had a complete anatomopathological response, except one case, where we found less than 5% tumor cells. In this patient a conservative surgical approach could be helpful.

Final TNM staging after neoadjuvant treatment is the best predictor of survival in rectal cancer, with pCR being a factor of good independent prognosis.[30] The main limitation of rectoscopy with biopsy is that it cannot assess nodal status or microscopic tumor. Considering that the primary tumor should not only be characterized by the grade of tumor regression but also by the grade of wall infiltration and that different studies show that a ypT0 status is related to low levels of residual nodal disease (0%–7%),[31,32] it is important to detect patients with a cCR to be able to apply less invasive therapies.

When suspecting a pCR based on radiological images (especially in PET-CT),[33] post-CRT rectoscopy offers the possibility of selecting patients for less invasive surgery.[20] These techniques offer the advantages of a shorter perioperative time and lower rates of morbidity and

mortality, although they have the drawback of leading to scarring and disruption of the rectal layers and therefore hindering further surgery.

There is mention in the literature of some authors advocate the "wait and see" strategy, whereby patients suspected with a cCR to the neoadjuvant treatment are spared from surgery and instead are followed up monthly for a year to rule out an underdiagnosed partial response or the presence of tumor recurrence. The main problem with this strategy lies, together with ethical issues, in the few studies existing in the literature and the contradictions between them.[34]

Our study has some limitations. First, the percentage of cCR is similar to that reported in the literature but the number of cases in our series is small. However, this is a single-center study, and we believe that a multidisciplinary committee should be set up to carefully study cases suspected with a cCR by unifying criteria and establishing action protocols.

CONCLUSION

The results of this study indicate that the relationship between endoscopic and histological findings could be determinants in the assessment of response to neoadjuvant treatment, with a view to considering more conservative surgical treatment. The biopsy results should always be interpreted together with the endoscopic findings. A negative biopsy for malignancy by itself is not useful in cases of non-cCR because decision making is hampered by their high percentage of false negatives. Further prospective studies are needed to evaluate this promising option.

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Conflicts of interest
There are no conflicts of interest.

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