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Pathologic response assessed by Mandard grade is a better prognostic factor than down staging for disease-free survival after preoperative radiochemotherapy for advanced rectal cancer

J. Suárez*, R. Vera†, E. Balén*, M. Gómez‡, F. Arias§, J. M. Lera*, J. Herrera* and C. Zazpe*

Departments of *General Surgery, †Medical Oncology, ‡Pathology and §Radiotherapy, Hospital de Navarra, Pamplona, Spain

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Abstract

Objective The reduction in tumour stage induced by full course radiotherapy plus chemotherapy is apparent from histological changes. The purpose of this study was to determine the rate of complete pathological response and to evaluate the prognostic value for disease free survival (DFS) and disease specific survival (DSS) of the response. The relation between pretreatment variables (age, gender, stage, tumour height and [carcinoembryogenic antigen (CEA)] and postsurgical variables was compared to the pathological response.

Method A total of 119 patients with stage II or III rectal cancer underwent surgery 6 weeks after neoadjuvant treatment. Group A included patients with a complete or good pathological response (Mandard grade I–II) and group B patients with a poor response (Mandard grade III–IV–V).The pretreatment endo-rectal ultrasound scan stage was compared with histopathology stage of the resected specimen. DFS and DSS were compared using the log-rank test.

Results All 119 patients (mean age 67.9 years, 83 males) underwent resection. The tumour was located in the upper, middle and lower third of the rectum in 11, 51 and 57 patients. 88 patients had a low anterior resection, 28 patients abdomino-perineal resection and three a Hartmann's operation. There was no postoperative death. The circumferential margin (CM) was involved in 10%. A complete pathological response was observed in 17 (14.2%) patients. Thirty-six (30.2%) patients had a group A and 83 a group B response. Group A showed DFS to be significantly higher than group B (log rank: $P = 0.007$). The DSS rate was not significantly different between the two groups (log rank $P = 0.113$). Down-staging was not related with DFS. No relation was found between pretreatment variables and response. A good pathological response was related to a lower rate of permanent colostomy but not with CM involvement or the number of lymph nodes.

Conclusion Tumour regression of grades I or II was a good indicator of DFS in locally advanced rectal cancer, treated by neoadjuvant chemotherapy and radiotherapy. Patients with a high regression grade were associated with a lower incidence of definitive stoma formation. The regression grade was shown to be a better prognostic factor than down-staging.

Keywords Rectal cancer, pathological response, pre-operative chemoradiotherapy

Introduction

Improved results in the treatment of rectal cancer have been due to the introduction of total mesorectal excision (TME) and of neoadjuvant treatment [1–3].

Neoadjuvant treatment can be given as short course radiotherapy, or long course radiotherapy combined with chemotherapy (CRT). The latter gives better control of the disease than the former [4,5], being associated with a reduction in tumour size and stage, not observed with short course radiotherapy.

The reduction in the tumour stage induced by full course CRT, apparent histologically has been classified [6,7]. These changes may be a better guide to prognosis than the pTNM classification.

The study evaluated the prognostic value of the histopathological response to neoadjuvant treatment, using Mandard's classification. Patients were divided into

Correspondence to: Dr Javier Suárez, Department of General Surgery, Hospital de Navarra, Irunlarrea 3, 31008 Pamplona, Spain.
E-mail: jsuareza@eresmas.com

Mandard's grade I–II (group A) and Mandard's grade III–IV–V (group B). Tumoral regression, was also studied in relation to the circumferential margin (CM) and the need for a colostomy.

Method

Between January 2001 and December 2006, 128 patients with locally extensive rectal cancer underwent surgery after neoadjuvant treatment with CRT. Nine with metastases were excluded and in one patient the tumour was not completely removed. There were therefore 119 patients in the study.

Preoperatively patients underwent colonoscopy, an abdominal CT scan, a chest X-ray and estimation of tumour markers. Staging was carried out by endo-rectal ultrasound scan (EUS), which was done in 101 patients. In 18 patients, magnetic resonance (MRI) was performed. The height of the tumour was established by flexible endoscopy. Tumours lying at or below 0 and 5 cm were defined as being in the lower third of the rectum, those between 6 and 10 cm in the middle third and those between 11 and 15 cm in the upper third.

Neoadjuvant treatment included radiotherapy (180 cGy/day) over 5 weeks to a dose of 4500 cGy; after which, the tumour area was over-printed by a margin of 2 cm to a total of 5040 cGy. Patients received concomitant fluoropyridine-based chemotherapy. Surgery was performed at an interval of 6 weeks following CRT. Patients with a tumour located in the lower or middle third had a total mesorectal excision. In patients with a tumour in the upper resection the mesorectum was removed to a distance of 5 cm beyond the tumour.

Histopathological staging

Histopathological examination of the resected specimen was performed according to an established protocol. On arrival in the laboratory, the pathologist inspected it to assess the quality of the mesorectal resection and the surface was painted with permanent ink and fixed in formalin over 24 h. The specimen was then photographed. Transverse sections (4 mm thick) were cut above, through and below the tumour and stained with haematoxylin and eosin. Sections were stained with cytokeratin antibodies to assure a complete pathological response. Distance between tumour and circumferential margin was measured in millimetres. If tumour growth was found within 1 mm of the CM, it was reported to be involved. Staging was carried out according to the TNM classification. The evaluation of the tumour response to neoadjuvant treatment was performed based on Mandard's classification (Table 1). Patients were divided into two groups, according to the pathological response. Group A included patients whose response was grade I and II. Group B included patients with grade III, IV or V downstaging.

Table 1 Mandard's classification.

Grade I	Complete regression
Grade II	Isolated cell nests
Grade III	More residual cancer cells but fibrosis still predominates
Grade IV	Residual cancer outgrowing fibrosis
Grade V	Absence of regressive changes

Table 2 Comparison between ultrasound (US) pretreatment TN stage and pathological TN stage.

	Pathological stage						
	T0,1N0	T2N0	T2N1	T3NO	T3N1	T4N0	T4N1
US stage							
T2N1(6)	1	1	3	1			
T3N0(56)	15	14	3	18	4	1	1
T3N1(34)	3	5	1	15	10		
T4N0(1)		1					
T4N1(4)	1			3			

Assessment of response was made with comparison to the pretreatment T,N determined by EUS (Table 2).

Follow up

During the first 2 years, patients were followed up at 3-monthly intervals, and 6 monthly after the third year. Tumour markers were tested at every visit. A chest X-ray was performed annually and a colonoscopy in the second and fifth year. Liver imaging was not requested routinely when the tumour markers were normal.

Tumour recurrence in the pelvis was considered to be local failure. The remaining recurrences (including pelvic bony metastases) were considered disseminated disease. Local failure was confirmed through compatible radiological imaging, raised marker levels and/or positron emission tomography (PET).

Statistical analysis

Ratio comparisons were made using the chi-square test. The quantitative variables were compared using the Mann–Whitney test. Disease free survival (DFS), cancer specific survival and overall survival rates were compared using the log-rank method SPSS Software System (version 11.0; SPSS, Chicago, Illinois, USA) for Windows.

Results

There were 119 patients of mean age 67.97 years (range 41–87) [83 males (69.7%)]. The tumour was located in the upper third of the rectum in 11 (9.2%), the middle in 51 (42.8%) and in the lower third in 57 patients (47.8%). A low anterior resection was performed in 88 patients, an abdomino-perineal resection in 28 and a Hartmann's operation in three patients. Surgical complications occurred in 33 (27.7%) patients. There was no postoperative death. The rate of CM involvement was 10% (12 cases). Group A included 17 (14.2%) patients (Mandard grade 1) and 19 (16.0%) grade 2, giving a total of 36 patients (30.2%) with a good response. Eighty-three patients had a poor response (group B).

Table 3 shows the pretreatment clinical variables of groups A and B. No differences were observed in age, sex, tumour level, rectal wall infiltration or CEA levels.

The mean duration of follow-up was 33.12 (3–73) months. Recurrence occurred in 20 (16.8%) patients. In three (2.5%), this was a local relapse and in 16 (13.4%) distant. One patient developed both a local and distant recurrence. All the patients who relapsed were in group B (24%) with none in group A experiencing a relapse. The DFS rates in group B were 91%, 83.6% and 73.8% at 1, 2 and 3 years of follow-up. Patients in group A showed a disease free survival rate significantly higher than patients in group B (log rank: $P = 0.007$) (Fig. 1). Nine patients died from the disease (0% *vs* 10.8%). The disease specific survival and overall survival rate were not significantly different between the two groups (log rank $P = 0.113$ and $P = 0.492$) (Fig. 2).

Of the 101 patients undergoing preoperative EUS, downstaging was observed in 61 (Table 2). Recurrence was observed in eight patients with downstaging and in six without. There was no relation between DFS and downstaging. While the Mandard grade of regression was related to DFS (log rank: $P = 0.007$) (see above).

Table 4 shows the relation of response to CM involvement, type of surgery, lymph nodes identification and patients not receiving postoperative chemotherapy. Group A showed a nonsignificant lower rate of CM involvement. The number of lymph nodes identified was similar in both groups. The number of patients with a permanent colostomy was higher in group B (31.3%) *vs* group A (13.8%) ($P = 0.046$). There was no difference in the percentage of patients receiving adjuvant chemotherapy between the groups.

Discussion

The use of preoperative neoadjuvant CRT, can reduce tumour bulk. Invasion of the rectal wall decreases and it

Table 3 Pretreatment clinical variables.

	Group A ($n = 36$)	Group B ($n = 83$)	*P*-value
Age (range)	67.3 (44–82)	68.2 (41–87)	0.645
Gender (M/F)	26/10	57/26	0.69
Presurgical staging (T2/T3/T4)	5/31/0	7/70/6	0.105
Tumour height			
Upper third	4	7	
Middle third	19	32	
Lower third	13	44	0.108
CEA (mean ng/ml)	10.6	12.9	0.741

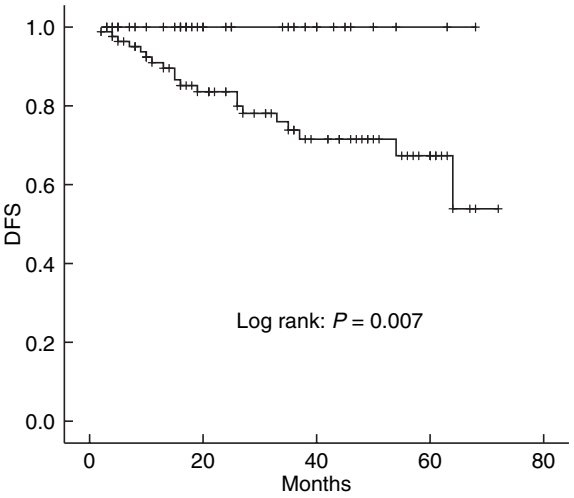

Figure 1 Comparison of DFS between group A and group B. Kaplan–Meier Life Table Analysis.

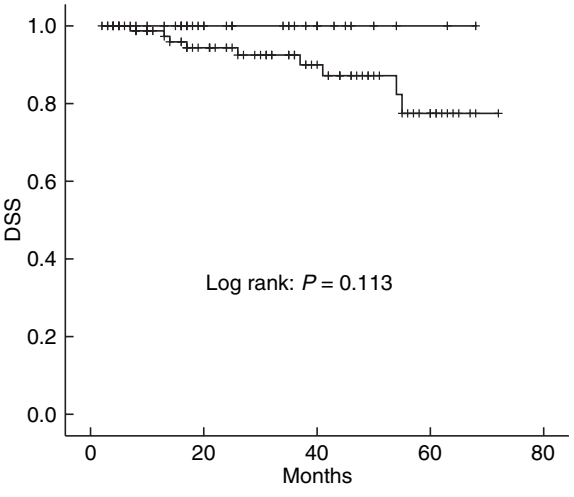

Figure 2 Comparison of DSS between group A and group B. Kaplan–Meier Life Table Analysis.

Table 4 Postsurgical variables.

	Group A (n = 36)	Group B (n = 83)	P-value
Type of surgery			
Permanent colostomy	5 (13.8%)	26 (31.3%)	
Anterior resection	31	57	0.046
No. resected lymph nodes	7.83	7.89	0.955
CM involvement	2* (5.5%)	10 (12%)	0.06
No adjuvant chemotherapy	6 (16.6%)	16 (19.2%)	0.95

CM, circumferential margin.
*Lymph node within a distance to CM shorter than 1 mm.

can even disappear [8] and the possibility of identifying nodes in the mesorectum may diminish [9]. Furthermore the macroscopic evaluation of disease becomes harder, due to difficulty in differentiating fibrosis from tumour. These occurrences, combined with the limited ability of preoperative imaging to stage both the T but, particularly, the N categories, render conventional TNM staging of limited value as a method to evaluate a tumour response.

The histological changes resulting from CRT offers another method of evaluating tumour regression [6,7,10].

There are several regression grading systems. The Association of Directors of Anatomic and Surgical Pathology [11] recommend a score of tumour regression (TR) proposed by Ryan [9]. In his report, he compared the prognostic value of Mandard's classification with a more reproducible three-grade score in which TRG 1 grouped the grades 1 and 2 of Mandard, TRG 2 was equivalent to Mandard grade 3 and TRG 3 to Mandard grades 4 and 5, confirming the prognostic value of both systems. In the present study, group A was similar to Ryan's TRG 1.

The percentage of patients with a complete pathological response varied according to the treatment. In patients receiving radiotherapy and 5-FU based chemotherapy, this was between 4% [12] and 33% [13]. In the present series, 17 (14.2%) patients had a complete pathological response (CPR), which is in agreement with the reports of others [14–17]. In an attempt to improve the CPR rate, some authors have used new drug regimens including oxaliplatin or irinotecan together with 5-FU [18,19].

Despite the differences in the classification of tumour regression in various studies, tumours with a complete or almost complete pathological response have a more favourable prognosis than the rest [14–17,20]. In our series, no patient in group A with tumour regression grades I and II developed recurrence, compared with 24% of group B who did so. There was also a higher DFS rate in group A (P = 0.007). No correlation was found between cancer specific survival and pathological response. This may be due to the short follow-up of our series.

In the subgroup of patients having EUS, the Mandard tumour regression grade was correlated with DFS, but down staging assessed by TNM was not. As a consequence, tumour regression is a better prognostic factor than down staging.

Some authors have been able to correlate presurgical characteristics including tumour size with the tumour CPR [21,22], although this was not confirmed by other studies [17] and other factors such as gender, age, tumour height, stage or degree of differentiation have not shown any correlation with CPR [14–16]. In the present study, the tumour size prior to surgery was not documented. None of the presurgery variables actually recorded showed any correlation with the treatment response, thus it is difficult using this approach to identify the patients who may benefit from neoadjuvant treatment. Some studies have identified biological factors which may predict the response to neoadjuvant treatment [23–25] taken together with clinical factors such as the prediction of CM threat to the meso-rectum, it might in future help to decide which patients could benefit most from neoadjuvant treatment.

Neoadjuvant CRT not only results in a better local control of disease [2], but also some authors have associated it with a higher rate of sphincter preserving surgery [26,27], although others were unable to confirm this finding [16,17,28]. Whether the decision to perform an abdomino-perineal resection should be made before CRT or after based on the treatment response remains controversial. Thus the end-point of sphincter preservation might become an indication of the effectiveness of CRT. In this study, group B had a higher percentage (just significant) of definitive colostomy formation.

The use of preoperative neoadjuvant CRT has also been associated with CM involvement and the number of lymph nodes identified in the surgical specimen [29–31]. In the present series, the CM was involved in 5.5% of patients in group A and 12% of group B, a difference which was nearly statistically significant (P = 0.06).

Preoperative CRT leads to a reduction in size and numbers of mesorectal lymph nodes [9]. But in the present study there was no difference in the number of nodes in groups A and B.

In conclusion, Mandard tumour regression grades I or II were found to be a good prognostic factor in locally advanced rectal cancer, treated by neoadjuvant CRT and major surgery. These grades appear to be associated with a lower incidence of permanent stoma formation. Regression grade was shown to be a better prognostic factor than down staging assessed by TNM staging.

References

1 Kapiteijn E, Marijnen CA, Nagtegaal ID *et al.* Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. *N Engl J Med* 2001; **345:** 638–46.

2 Sauer R, Becker H, Hohenberger W *et al.* Preoperative versus postoperative chemoradiotherapy for rectal cancer. *N Engl J Med* 2004; **351:** 1731–40.

3 Improved survival with preoperative radiotherapy in resectable rectal cancer. Swedish Rectal Cancer Trial. *N Engl J Med* 1997; **336:** 980–7.

4 Bosset JF, Collette L, Calais G, Mineur L, Maingon F, Radosevic-Jelic L, Daban A, Bardet E, Beny A, Ollier JC. Chemotherapy with preoperative radiotherapy in rectal cancer. *N Engl J Med* 2006; **355:** 1114–23.

5 Gerard JP, Bonnetain F, Conroy T, Chapet O, Bouche O, Closon-Dejardin MT, Untereiner M, Leduc B, Francois L, Bedenne L. Preoperative (preop) radiotherapy (RT)/–5FU/folinic acid (FA) in T3-4 rectal cancers: results of de FFCD 9203 randomized trial. ASCO Meeting Abstracts, 1 June 2005: 3504.

6 Dworak O, Keilholz L, Hoffmann A. Pathological features of rectal cancer after preoperative radiochemotherapy. *Int J Colorectal Dis* 2000; **43:** 1075–83.

7 Mandard AM, Dalibard F, Mandard A *et al.* Pathologic assessment of tumor regression after preoperative chemoradiotherapy of esophageal carcinoma. *Cancer* 1994; **73:** 2680–6.

8 Bozzetti F, Andreola S, Rossetti C, Zucali R, Meroni E, Baratti D, Bertario L, Doci R, Gennari L. Preoperative radiotherapy for resectable cancer of the middle-distal rectum: its effect on the primary lesion as determined by endorectal ultrasound using flexible echo colonoscope. *Int J Colorectal Dis* 1996; **11:** 283–6.

9 Ryan R, Gibbons D, Hyland JMP, Treanor D, White A, Mulcahy HE, O'Donoghue DP, Moriarty M, Fennelly D, Sheahan K. Pathological response following long-course neoadjuvant chemoradiotherapy for locally advanced rectal cancer. *Histopathology* 2005; **47:** 141–6.

10 Rullier A, Laurent C, Vendrely V, Le Bail B, Bioulac-Sage P, Rullier E. Impact of colloid response on survival after preoperative radiotherapy in locally advancer rectal carcinoma. *Am J Pathol* 2005; **29:** 602–6.

11 Jass JR, O'Brien MJ, Riddell RH, Snover DC, on behalf of the Association of Directors of Anatomic and Surgical Pathology. Recommendations for the reporting of surgically resected specimens of colorectal carcinoma. *Hum Pathol* 2007; **38:** 537–45.

12 Boulis-Wassif S, Gerard A, Loygue J, Camelot D, Buyse M, Duez N. Final results of a randomized trial on the treatment of rectal cancer with preoperative radiotherapy alone or in combination with 5-fluorouracil, followed by radical surgery. Trial of the European organization on Research and Treatment of cancer Gastrointestinal Cooperative Group. *Cancer* 1984; **53:** 1811–8.

13 Mehta VK, Poen J, Ford F, Edelstein PS, Vierra M, Bastidas AJ, Young H, Fisher G. Radiotherapy, concomitant protracted-venous-infusion 5-fluorouracil, and surgery for ultrasound-staged T3 or T4 rectal cancer. *Dis Colon Rectum* 2001; **44:** 52–8.

14 Biondo S, Navarro M, Marti-Rague J, Arriola E, Pares D, Del Río C, Cambray M, Novell V. Response to neoadjuvant therapy for rectal cancer: influence on long-term results. *Colorectal Dis* 2005; **7:** 472–9.

15 Rödel C, Martus P, Papadoupolos T, Füzesi L, Klimpfinger M, Fietkau R, Liersch T, Hohenberger W, Sauer R, Witekind C. Prognostic significance of tumor regression after preoperative chemoradiotherapy for rectal cancer. *J Clin Oncol* 2005; **23:** 8688–96.

16 García-Aguilar J, Hernández de Anda E, Sirivongs P, Lee SH, Madoff RD, Rothenberger DA. A pathologic complete response to preoperative chemoradiation is associated with lower local recurrence and improvedsurvival in rectal cancer patients treated by mesorectal excision. *Dis Colon Rectum* 2003; **46:** 298–304.

17 Theodoropoulos G, Wise WE, Padmanabhan A, Kerner BA, Taylor CW, Aguilar PS, Khanduja KS. T-level downstaging and complete pathologic response after preoperative chemoradiation for advanced rectal cancer result in decreased recurrence and improved disease-free survival. *Dis Colon Rectum* 2002; **45:** 895–903.

18 Mehta V, Cho C, Ford JM *et al.* Phase II trial of preoperative 3D conformal radiotherapy, protracted venous infusion 5-fluorouracil, and weekly CPT-11, followed by surgery for ultrasound staged T3 rectal cancer. *Int J Radiat Oncol Biol Phys* 2003; **55:** 132–7.

19 Rödel C, Grabenbauer GG, Papadopoulos T, Hohenberger W, Schmoll HJ, Sauer R. Phase I/II trial of capecitabine, oxaliplatin, and radiation for rectal cancer. *J Clin Oncol* 2003; **21:** 2098–104.

20 Guillem JG, Chessin DB, Cohen AM *et al.* Long-term oncologic outcome following preoperative combined modality therapy and total mesorectal excision of locally advanced rectal cancer. *Ann Surg* 2005; **241:** 829–36.

21 Janjan NA, Khoo VS, Abbruzzese J *et al.* Tumor downstaging and sphincter preservation with preoperative chemoradiation in locally advanced rectal cancer: The MD Anderson Cancer Center experience. *Int J Radiat Oncol Biol Phys* 1999; **44:** 1027–38.

22 Willett CG, Warland G, Coen J, Shellito PC, Compton CC. Rectal cancer: the influence of tumor proliferation on response to preoperative irradiation. *Int J Radiat Oncol Biol Phys* 1995; **32:** 57–61.

23 Rau B, Sturm I, Lage H *et al.* Dynamic expression profile of p21WAF1/CIP1 and Ki-67 predicts survival in rectal cancer treated with preoperative radiochemotherapy. *J Clin Oncol* 2003; **21:** 3391–401.

24 Rödel C, Grabenbauer GG, Papadopoulos T, Bigalke M, Gunther K, Schick C, Peters A, Sauer R, Rodel F. Apoptosis as a cellular predictor for histopathologic response to neoadjuvant radiochemotherapy in patients with rectal cancer. *Int J Radiat Oncol Biol Phys* 2002; **52:** 294–303.

25 Scott N, Hale A, Deakin M, Hand P, Adab FA, Hall C, Williams GT, Elder JB. A histopathologic assessment of the

response of rectal adenocarcinoma to combination chemoradiotherapy: relationship to apoptotic activity, p53 and bcl-2 expression. *Eur J Surg Oncol* 1998; **24:** 169–73.

26 Rouanet P, Fabr JM, Dubois JB, Dravet F, Saint Aubert B, Pradel J, Ychou M, Solassol C, Pujol H. Conservative surgery for low rectal carcinoma after high-dose radiation. Functional and oncological results. *Ann Surg* 1995; **221:** 67–73.

27 Ueno H, Mochizuki H, Hashiguchi Y, Ishikawa K, Fujimoto H, Shinto E, Hase K. Preoperative paramenters expanding the indication of sphincter preserving surgery in patients with advanced local cancer. *Ann Surg* 2004; **239:** 34–42.

28 Brown CL, Ternent CA, Thorson AG, Christensen MA, Blatchford GJ, Shashidharan M, Haynatzky GR. Response to preoperative chemoradiation in stage II and III rectal cancer. *Dis Colon Rectum* 2003; **46:** 1189–93.

29 Wibe A, Rendedal PR, Svensson E, Norstein J, Eide TJ, Myrvold HE, Soreide O. Prognostic significance of the circumferential resection margin following total mesorectal excision for rectal cancer. *Br J Surg* 2002; **89:** 327–34.

30 Birbeck KF, Macklin CP, Tiffin NJ *et al.* Rates of circumferential resection margin involvement vary between surgeons and predict outcomes in rectal cancer surgery. *Ann Surg* 2002; **235:** 449–57.

31 Nagtegaal ID, Marijnen CA, Kranenbarg EK. Circumferential margin involvement is still an important predictor of local recurrence in rectal carcinoma: not one millimetre but two millimetres is the limit. *Am J Surg Pathol* 2002; **26:** 350–7.