Pathologic Response of Primary Rectal Cancer to Oxaliplatin-Based Chemotherapy

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ABSTRACT

Management of stage IV rectal cancer is controversial, and different strategies may be useful. Preoperative chemotherapy for liver metastases might cause pathologic changes over the primary rectal tumor. In this study, the authors show the pathologic regression of the primary rectal tumor after neoadjuvant chemotherapy treatment. Patients suffering stage IV rectal cancer underwent surgery after oxaliplatin-based chemotherapy. Age, gender, type of surgery, carcinoembryonic antigen (CEA) level, presence of metastatic disease in one or multiple organs, ypT, ypN, and circumferential resection margin (CRM) were evaluated. Pathologic response of the primary tumor was estimated by using three conventional grading systems and a semiquantitative system assessed by the amount of viable cells out of the total tumor area macroscopically described. Fibrosis, necrosis, and colloid response were evaluated with a semiquantitative system. A complete pathologic response (ypTO) was found in one patient. A good response was observed in the 41.6% of the cases with all grading systems. Presence of fibrosis in the primary tumor was found in six cases. No patient showed CRM involvement. One patient developed a local recurrence. Oxaliplatin-based chemotherapy for stage IV rectal cancer provides high rates of pathologic regression in the rectal tumor and may allow surgery without CRM involvement.

KEYWORDS: Rectal cancer, neoadjuvant radiotherapy, neoadjuvant chemotherapy, pathologic regression

Objectives: Upon completion of this article, the reader should be familiar with the pathologic response of primary colorectal cancers to chemotherapy.

Management of rectal cancer with intention to cure in the presence of metastatic disease is controversial. However, some issues are particularly relevant in the development of a treatment strategy.

First, the benefit obtained with perioperative chemotherapy (ChT) in the treatment of the metastatic disease¹ and with neoadjuvant chemoradiotherapy (ChRT) over the primary tumor has not been determined. No survival benefit related to preoperative radio-

therapy was observed from the Norwegian Rectal Cancer Registry² and no benefit related to preoperative ChRT was reported by Assumpcao et al.³

Second, the timing of surgery is unclear. The decision about a simultaneous or staged resection may be controversial. Other authors propose to perform the liver resection prior to rectal surgery.⁴ Thus, in stage IV rectal cancer, an individualized approach should be undertaken by a multidisciplinary team.

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The pathologic response of the primary tumor to neoadjuvant ChRT is well known in stage II–III rectal cancer.^{5,6} Many grading systems have been proposed to evaluate pathologic response to neoadjuvant treatment. The most commonly used are the Mandard, Dworak, and Ryan classification systems, which evaluate the proportion of fibrosis versus residual cancer cells.^{7–9} This issue has been poorly studied in stage IV rectal cancer, as has the characteristics of the response of the primary tumor to neoadjuvant ChT alone. Fibrosis is not characteristically a specific feature of pathologic response to ChT; hence, some of those classifications might not be useful. Instead, it might be more accurate to quantify the percentage of viable tumor cells.

We analyzed the tumor regression grade (TRG) and the type of response after neoadjuvant ChT or ChRT in patients with stage IV rectal cancer.

MATERIAL AND METHODS

Between January 2001 and December 2009, 25 patients with stage IV rectal cancer underwent surgery for rectal tumor after neoadjuvant ChT (Group A) or after ChRT (Group B). Surgery was performed to affect a cure or to offset symptoms. In this article, we show the histologic regression changes in the rectal surgical specimen.

Group A was comprised of patients who received 4 to 12 cycles (median: 6.6) of 5-FU-oxaliplatin-based ChT with or without monoclonal antibodies (Bevacizumab in three patients and Cetuximab in five) prior to undergoing resection of the rectal tumor. Group B consisted of patients undergoing rectal resection after fluoropyrimidine-based ChT plus radiotherapy (5040 cGy).

The diagnosis of rectal cancer was confirmed after endoscopic biopsy. The height of the tumor was established by endoscopy in retrieval. Radiologic staging included computed tomography (CT) of the abdomen and pelvis and CT of the thorax or by positron emission tomography (PET). The decision regarding treatment was made by the Digestive Oncology Committee of Hospital de Navarra. Age, gender, primary tumor location, administration of postoperative ChT, type of surgery, carcinoembryogenic antigen (CEA) level, presence of metastatic disease in one or multiple organs, unilobar or bilobar liver involvement, and pathologic data were evaluated in both groups. Tumor recurrence in the pelvis was considered to be local failure. The remaining recurrences were considered disseminated disease. Overall survival was calculated based on time of diagnosis.

Histopathologic Review

Specimens were evaluated according to an established protocol. Fresh surgical specimens were examined to

assess the quality of the mesorectal excision and afterwards, fixed in 4% formaldehyde for a minimum of 48 hours. After fixation the mesorectal margin was inked and the specimens serially sectioned (in 1-cm slices). When residual tumor was visible a minimum submission of four blocks was recommended, but if it was not confirmed, the whole suspicious area was submitted. All mesorectal lymph nodes were submitted for their histologic examination and the circumferential resection margin (CRM) involvement was evaluated.

If no residual tumor cells were found, additional three level sections were performed of each block as well as an additional immunohistochemistry for keratin 20. All hematoxylin-eosin slides were reviewed by an experienced pathologist.

Pathologic response of the primary tumor was estimated by using the three grading systems most frequently described in the literature,^{7–9} and also a semiquantitative system assessed by the amount of viable cells out of the total tumor area macroscopically described (Table 1). Cases classed as TRG 0–1 according to Mandard's classification, TRG 1 according to Ryan's classification, TRG 3–4 according to Dworak's classification and with less than 5% of residual tumor were considered to have good pathologic response. The remaining cases were considered to have poor response.

The tumor area included areas of treatment-related changes: fibrosis, necrosis, and colloid response. For this study, two subsets were analyzed with a semiquantitative system: < 25% of the tumor (absence) and > 25% of the tumor (presence) (Table 2).

Statistical Analysis

Ratio comparisons were made using the chi-square test. The nonparametric variables were compared using the Mann-Whitney test. Survival rates were compared using the log-rank method. SPSS Software System (14.0; SPSS, Chicago, IL) for Windows was used for statistical calculations.

RESULTS

Patient characteristics are given in Table 3. Both groups were comparable regarding age, gender, tumor location, presence of metastatic disease in one or multiple organs, unilobar or bilobar liver involvement, administration of postoperative ChT, CEA level, and type of surgery. The CRM involvement was much higher in group B (0 vs 38.4%; $P = .006$) and the number of lymph nodes identified was significantly lower after ChRT (14.5 vs 9; $P = .022$). There were significant differences in ypT-stage (Table 3). Median of survival was 48.8 months for group A and 28.7 months for group B (Log-rank: $P = .100$). One patient in group A (8.3%) and two in group B (15.3%) showed a local relapse.

Table 1 Classification Systems of the Pathologic Response

Mandard's classification	Grade 1	No viable cancer cells
	Grade 2	Isolated cancer cells
	Grade 3	Residual cancer cells but fibrosis still predominates
	Grade 4	Significant fibrosis outgrown by cancer
	Grade 5	Absence of regressive cancer
Ryan's classification	Grade 1	Mandard 1 and 2
	Grade 2	Mandard 3
	Grade 3	Mandard 4 and 5
Dworak's classification	Grade 0	No regression
	Grade 1	Dominant tumor mass with obvious fibrosis in 25% or less of the tumor mass
	Grade 2	Dominant tumor mass with obvious fibrosis in 26–50% or less of the tumor mass
	Grade 3	Dominant fibrosis outgrowing the tumor mass (more than 50% tumor regression)
	Grade 4	Complete regression (no viable tumor cells, only fibrotic mass)
Semiquantitative system	Grade 1	Less than 5% of viable cells
	Grade 2	5 to 49% of viable cells
	Grade 3	50% or more of viable cells

There was no significant difference with respect to the intensity of the pathologic response of the primary tumor to treatment, though higher rates of good response were achieved in group A with three grading systems: Mandard, Ryan, and the semiquantitative system (41.6% vs 7.6%; $P = .129$). One patient in group A showed a complete pathologic response. One patient in group B was classified as poor response in three grading systems, but as a good response in Dworak's classification (Table 4).

Regarding the type of response, presence of fibrosis in the primary tumor was found in 6 patients of group A and in 12 patients of group B (50% vs 92.4%; $P = .021$). There were differences in the necrosis grading regarding the colloid response (Table 2).

DISCUSSION

Recently, Gervaz et al¹⁰ compared the histologic response to ChT in liver metastases and the primary colorectal tumor, but found little evidence of the pathologic response of the rectal tumor after preoperative ChT. The target of this study was to evaluate the TRG of the primary rectal tumor after neoadjuvant ChT. Because the number of cases was small, the comparison with the ChRT group was done in reference

to similar patients, not differences between both types of treatments.

Five patients in group A and one patient in group B (41.6% vs 7.6%; $P = .129$) had good pathologic response according to three classifications. Though the pathologic regression of the primary rectal cancer to ChT is poorly studied, these data confirm this issue.

Pathologic response in group B is less than the response observed by our group in patients with stage II–III rectal cancer after neoadjuvant treatment with the same ChRT regimen. The rate of good response was 30% for stage II–III rectal cancer¹¹ and 7.6% in the present series of patients with stage IV rectal cancer. A similar rate of good response (5.7% of complete or near complete response) was found by Assumpcao et al³ in stage-IV rectal cancer. Previous reports found poor pathologic response to neoadjuvant ChRT in large tumors.¹² Usually, a large primary tumor is found in the setting of stage IV rectal cancer; this fact could explain the low rate of pathologic regression in group B.

Moreover, there are differences in the type of pathologic response. Fibrosis is a characteristic found after ChRT, but is not common after ChT. In our series, there was a significant difference with respect to appearance of fibrosis (50% vs 92.4%; $P = .05$). That is why no

Table 2 Evaluation of the Type of Pathologic Regression in Both Groups

Pathologic Features	Percentage	Group A	Group B	<i>p</i> value
Fibrosis	0–25%	6 (50%)	1 (7.6%)	.021
	>25%	6 (50%)	12 (92.4%)	
Necrosis	<25%	11 (91.6%)	11 (84.6%)	.595
	>25%	1 (8.3%)	2 (15.3%)	
Colloid response	0–25%	9 (75%)	10 (76.9%)	.721
	>25%	3 (24.9%)	3 (23%)	

Table 3 Comparison of Clinical and Pathologic Variables

Patient Characteristics	Group A	Group B	p value
Age	63 (44–75)	67 (51–79)	.224
Gender			
Males	11 (91.6%)	8 (61.5%)	.196
Females	1 (8.3%)	5 (38.4%)	
Postsurgery ChT	10 (83.3%)	11 (84.6%)	.930
Tumor location			
0–5 cm	4 (33.3%)	5 (38.4%)	.834
6–10 cm	5 (41.6%)	6 (46.1%)	
11–15 cm	3 (25%)	2 (15.3%)	
Type of surgery			
Anterior resection	10 (83.3%)	7 (53.8%)	.106
Abdomino-perineal resection (APR)	2 (16.6%)	2 (15.3%)	
Ultra-low Hartmann	0	4 (30.7%)	
Metastatic lesion			
Single organ	9 (75%)	13 (100%)	.192
Multiple organs	3 (25%)	0	
Liver involvement			
Unilobar	3 (25%)	5 (45.4%)	.555
Bilobar	9 (75%)	6 (54.5%)	
Carcinoembryogenic antigen level	357.7	57.9	.282
Circumferential resection margin involvement	0	5 (38.4%)	.006
Lymph node retrieval	14.5	9	.022
ypT			
0	1 (8.3%)	0	
1	1 (8.3%)	0	.050
2	0	0	.050
3	10 (83.3%)	11 (84.6%)	
4	0	2 (15.3%)	
ypN			
0	5 (41.6%)	3 (23%)	.022
1	7 (58.3%)	10 (77%)	

TRG 3 according to Mandard's classification (fibrosis predominates over residual cancer) and no 0 TRG 2 of Ryan's classification could be found in group A. There were no differences in necrosis and colloid response.

Although many pathologic-response grading systems have been proposed, none seems to be universally accepted. Nowadays we face such a wide range of therapeutic options that we should encourage implementing pathologic regression grading. In our opinion, the use of systems such as the quantification of the amount of viable cells versus the total tumor area, which quantify tumor regression independently of the type of treatment applied, might be more useful than classifications based in the proportion between fibrosis and tumor cells.

In the present study, there were significant differences in ypT-stage and in CRM involvement (Table 3).

This may be related to the high rate of good pathologic regression in group A. In addition, the number of lymph nodes identified in group B was less than in group A. Recent reports have found that preoperative ChRT for rectal cancer results in a reduction in the number of lymph nodes identified.¹³ This, together with the results found in the four patients with a palliative Hartmann procedure, could explain the lower number of lymph nodes retrieved in group B patients.

With respect to the oncologic outcome, there were no significant differences in local recurrence rates or survival.

Although the aim of the study was not to compare two different ways to treat stage IV rectal cancer, the high rates of good local response, the lower grade of pT-stage, and the better rates of CRM involvement—without differences in local recurrence

Table 4 Comparison of the Pathologic Regression Grades with the Four Systems and Comparison of the Good Response Rates

System	Group A	Group B	p value	Impression	Group A	Group B	p value
Mandard							
I	1 (8.3%)	0	.731	Good response	5 (41.6%)	1 (7.6%)	.129
II	4 (33.3%)	1 (7.6%)					
III	0	9 (69.2%)					
IV	6 (50%)	3 (23%)		Poor response	7 (58.3%)	12 (92.3%)	
V	1 (8.3%)	0					
Ryan							
I	5 (41.6%)	1 (7.6%)	.484	Good Response	5 (41.6%)	1 (7.6%)	.129
II	0	11 (84.3%)					
III	7 (58.3%)	1 (7.6%)		Poor response	7 (58.3%)	12 (92.3%)	
Dworak							
1	6 (50%)	0	.501	Poor response	7 (58.3%)	11 (84.8%)	.309
2	1 (8.3%)	11 (84.8%)					
3	4 (33.3%)	2 (15.2%)					
4	1 (8.3%)	0		Good response	5 (41.6%)	2 (15.2%)	
Viable cells							
< 5%	5 (41.6%)	1 (7.7%)	.794	Good response	5 (41.6%)	1 (7.6%)	.129
5–49%	1 (8.3%)	8 (61.6%)					
> 50%	6 (50%)	4 (30.8%)		Poor response	7 (58.3%)	12 (92.3%)	

after neoadjuvant ChT—may indicate that ChT for metastatic disease may be useful as neoadjuvant treatment of the primary tumor; hence, radiotherapy could be avoided in selected cases.

In conclusion, oxaliplatin-based ChT for stage IV rectal cancer provides high rates of pathologic regression in the primary tumor with less fibrosis than neoadjuvant ChRT. Our preliminary results and this hypothesis should be confirmed in future trials.

DISCLOSURE

The authors have no conflicts to disclose with respect to this manuscript.

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