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Original Research

Local recurrence after five years is associated with preoperative chemoradiotherapy treatment in patients diagnosed with stage II and III rectal cancer

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HIGHLIGHTS

- Local recurrence after rectal cancer resection for stage II and III was diagnosed significantly later after preoperative chemoradiotherapy.
- The benefit of neoadjuvant chemoradiotherapy in local control of stage II and III rectal cancer was lower at 120 months as compared to 60 months.
- Follow-up longer than 5 years is needed for evaluating definitive results in patients treated with neoadjuvant chemoradiation.

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ABSTRACT

Aim: To asses the moment of local recurrence and its influence on the appraisal of the results of neoadjuvant chemoradiotherapy (CRT).

Methods: We evaluated 317 patients with a preoperative diagnosis of stage II or III rectal cancer who underwent rectal resection. Gender, age, neoadjuvant treatment, circumferencial resection margin, adjuvant treatment, pretreatment carcinoembryonic antigen level, tumor location, TNM stage, lymph node retrieval, abdominoperineal resection, and lymphatic or vascular infiltration were registered prospectively. Follow-up was performed to detect local or systemic recurrences. Timing of local recurrence (LR) in regard to analyzed variables was performed by using analysis of variance. To evaluate the influence of late local recurrence (LLR) on the results of neoadjuvant CRT, we performed a log-rank test censoring all observations at 60 and at 120 months.

Results: After a mean follow-up of 73.6 months (range, 1–171), 68 patients developed a recurrence. Twenty-three patients developed LRs (6.9%), and 5 developed LLRs. The earliest relapse was diagnosed 4 months after rectal surgery, and the latest was diagnosed 120 months after surgery. Patients who underwent neoadjuvant CRT developed LR significantly later than patients without neoadjuvant CRT (51.8 vs 13.5 months; $P = 0.002$). LR rates in patients who underwent preoperative CRT and those who did not were 9.2% and 3.5% (difference, 5.7%), respectively, after censoring all observations at 60 months and 9.2% and 6.1% (difference, 3.1%) after censoring all observations at 120 months.

Conclusion: Local recurrence was diagnosed significantly later in patients treated with neoadjuvant CRT. Follow-up longer than 5 years is needed to evaluate definitive results in patients treated with neoadjuvant CRT.

Core tip: The local recurrence rate is one of the most important parameters in evaluating cancer treatment results. Results from earlier investigational studies showed that most recurrences developed in the first 2 years. Results from more recent investigational studies, such as the present one, show that the introduction of perioperative radiotherapy delays the development of local recurrence. Therefore, for a proper evaluation of the results, a follow-up longer than 5 years is needed.

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1. Introduction

Most surveillance programs for patients treated for rectal cancer end 5 years after treatment, although screening for detecting second colorectal tumors is recommended after this period [1,2]. The aim of these programs is to identify asymptomatic metastases or local recurrences (LRs) at a stage suitable for curative treatment. Another purpose of these programs is to evaluate and compare results of different treatments.

According to the literature, most colorectal cancer tumor recurrences develop within 5 years after surgery [2], and 80% of local relapses are detected during the first 2 years after rectal resection [3]. Nevertheless, results from the most recent reports show that long-term follow-up beyond 5 years increases the number of late local recurrences (LLRs) that develop [4], particularly in patients treated with perioperative chemoradiotherapy (CRT) [5].

The aim of this study was to asses when LR develops and the factors involved in its appearance in patients with rectal cancer and to evaluate the influence of LLRs on the appraisal of the results of neoadjuvant CRT.

2. Material and methods

The present study was approved by the Research Ethics Committee (Cómite Etico de Investigación Clínica) of the Complejo Hospitalario de Navarra, Pamplona, Spain. Patients were identified from a prospective data set of patients who underwent surgery for rectal cancer. Between January 2001 and December 2012, 317 patients received a preoperative diagnosis of stage II or III rectal cancer and underwent rectal resection with or without preoperative CRT. Patients with stage I and stage IV rectal cancer, those treated with a short course of radiotherapy, and those treated with local resection were excluded.

Preoperatively, patients underwent colonoscopy, abdominal and pelvic computed tomography, and chest radiography, and tumor markers were assessed. Local staging was performed by means of endorectal ultrasonography and/or pelvic magnetic resonance imaging. Neoadjuvant treatment included radiotherapy (180 cGy/day) over 5 weeks to a dose of 4500 cGy. Subsequently, the tumor area received a total of 5040 cGy. Patients received concomitant fluoropyrimidine-based chemotherapy (ChT). Surgery was performed 6–8 weeks after CRT. Total mesorectal excision was performed for tumors located in the lower and middle rectum. The mesorectum was removed to a distance of 5 cm beyond the tumor for tumors located in the upper rectum. Histopathologic examination was performed according to an established protocol previously described [6]. Patient data, including gender, age, neoadjuvant treatment, pretreatment carcinoembryonic antigen (CEA) level, circumferencial resection margin (CRM), adjuvant treatment, tumor location, TNM-stage, lymph node retrieval, abdominoperineal resection, and lymphatic or vascular infiltration were registered prospectively.

Patients were categorized by age 75 and lymph node retrieval by 12 nodes, and CEA level was dichotomized according to its normal or elevated value. Tumors at or below 0 and 5 cm were categorized as lower-third tumors of the rectum; those between 6 and 10 cm, as middle-third tumors; and those between 11 and 15 cm, as upper-third tumors.

During the first 2 years, patients were followed up at 3-month intervals, and they were followed up at 6-month intervals thereafter. CEA level was tested at every visit, and chest and abdomen computed tomography was performed annually. After 5 years, visits and explorations were performed annually at the discretion of the attending physician. Colonoscopy was performed 1 year after surgery; subsequent colonoscopy follow-up was dictated by the findings of the previous colonoscopy results until recurrence, death, or age greater than 75 years. Clinical records were reviewed, and all recurrences and causes of death were entered in the database.

The patients who were not to undergo preoperative CRT were selected at the multidisciplinary meeting of our institution. Selection was based on tumor location, absence of threat of circumferential margin visible at magnetic resonance imaging, age, and performance status. Adjuvant ChT was administered according to the oncologist criteria and was not given to unfit patients and/or with old age and after pathological complete response.

LR was defined as tumor recurrence in the pelvis. LLR was defined as LRs diagnosed more than 5 years after primary surgery.

The continuous variables were described as means and were compared by using analysis of variance. A multivariate analysis was performed for all variables with $P < 0.2$ after univariate regression. LR-free survival in patients who had received neoadjuvant treatment and those who had not was compared by using a log-rank test. To evaluate the influence of LLR on the results of neoadjuvant CRT, we performed a log-rank test censoring all observations at 60 months and at 120 months. We used software (IBM SPSS Statistics 20 system for Windows) for statistical calculations.

3. Results

Patient characteristics are shown in Table 1. One-hundred and ninety patients were stage II (123 received preoperative CRT) and

Table 1
Patient demographics.

Clinical variable	n	%	Mean
Total N	317	100	
Age at diagnosis, yr			
>75	94	29,7	68,32
<75	223	70,3	
Gender			
Male	219	69,1	
Female	98	30,9	
Neoadjuvant treatment			
No	119	37,5	
Yes	198	62,5	
Adjuvant treatment			
No	104	32,8	
Yes	213	67,2	
Pathologic stage			
0	27	8,5	
I	53	16,7	
II	118	37,2	
III	119	37,5	
CRM			
Negative	282	89,0	
Positive	35	11,0	
Distance form anal verge, cm			
11–15	86	27,1	
6–10	112	35,3	
0–5	119	37,5	
Number of harvested lymph nodes			
<12	161	50,8	12,97
>12	156	49,2	
Initial CEA, ng/ml			
<5	229	72,2	9,71
>5	80	25,2	
Total	309	97,5	
Not available	8	2,5	
APR			
No	257	81,1	
Yes	60	18,9	
Lymphovascular invasion			
No	242	76,3	
Yes	75	23,7	