Analysis of Early Postoperative Morbidity Among Patients with Rectal Cancer Treated with and without Neoadjuvant Chemoradiotherapy

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Background: The impact of neoadjuvant treatment and their subsequent early complications in the treatment of rectal cancer has not been adequately assessed. The aim of this prospective study was to evaluate early postoperative morbidity and mortality among patients with rectal cancer treated with adjuvant radiotherapy and chemotherapy followed by surgery, compared with patients treated with surgery alone. We also identified independent risk factors associated with early major complications.
Methods: Between 1995 and 2004, 273 consecutive patients underwent treatment for rectal cancer. A total of 170 patients (group A) received preoperative radiotherapy with a total of 45–50.4 Gy (180 cGy per day) and 5-fluorouracil-based chemotherapy, followed by surgery; 103 patients (group B) were treated with surgery alone. Dependent variables related to patients, treatment, radiotherapy, and tumor were analyzed.
Results: Both groups were similar with regard to age, sex, body mass index, American Society of Anesthesiologists (ASA) score, and tumor location but not for ileostomy (27% in group A vs. 6.8% in group B). The number of complications was similar in both groups (43.1% in group A vs. 44.6% in group B). No differences in wound infection (8.2% vs. 7.8%), intraabdominal abscess (4.7% vs. 4.9%), anastomotic dehiscence (4.2% vs. 3.8%), postoperative hemorrhage (3.5% vs. 3.9%), urinary complications (6.5% vs. 4.9%), paralytic ileus (8.9% vs. 9.7%), or general complications (7.1% vs. 9.6%) were found. The global mortality in the first 30 days after surgery was .7%. An ASA score of III–IV and surgery duration longer than 3 hours were identified as independent prognostic factors for early complications.
Conclusions: Preoperative chemoradiation in patients with rectal cancer treated with surgery is not associated with a higher incidence of early postoperative complications. The patient~s preoperative clinical condition and lengthy surgery time are prognostic factors for early complications.
Key Words: Rectal cancer—chemoradiation.

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The therapeutic aim in rectal adenocarcinoma treatment is to attain cure, longer disease-free survival time with good quality of life, and reduction of local recurrence of disease, all while minimizing the risk of complications. Surgical treatment is the basis of therapy in those cases where good mesorectal excision is achieved, following the criteria established by Heald et al. in 1982.[1–3] On many occasions, depending on the extent of tumor, neoadjuvant chemotherapy is required.

Better control of local disease, reduced therapeutic toxicity, a possible increase in the proportion of patients having surgery with sphincter preservation, and a slight increase in survival time are the advantages offered by neoadjuvant therapy in comparison with postoperative adjuvant therapy.[4–10] It seems that the response rate after treatment with preoperative chemoradiotherapy is approximately double that after radiotherapy alone (20% vs. 10%).[10] Some specific modifications of the radiotherapy technique, as well as an increase in the time elapsed between the end of radiotherapy and surgery, may increase the number of complete responses.[11]

Nowadays, some surgeons consider that neoadjuvant therapy increases the incidence of early postoperative complications, especially causing a higher incidence of anastomotic leakage. However, evidence is derived only from experimental studies.[12,13] Some published studies describe the influence of radiation on early postoperative morbidity and mortality. However, the existing range of methodologies, inclusion criteria, and therapeutic modalities makes it difficult to analyze such an influence.[14–18] Some studies also show mortality associated with adjuvant combined therapy,[19,20] as well as toxicity and surgical reintervention because of intestinal obstruction[19] and disturbances in bowel habit and incontinence,21,22 associated with radiation.

The purpose of this study was to analyze the early postoperative complications in a group of patients treated with preoperative chemoradiotherapy and surgery, as compared with another group treated with surgery alone, and to identify possible prognostic factors associated with postoperative morbidity.

PATIENTS AND METHODS

Design

Between January 1995 and December 2004, 273 patients diagnosed with rectal adenocarcinoma (tumor margin <16 cm from the anal verge) were treated in our hospital. They were attended by a multidisciplinary team made up of oncologists, radiotherapists, and surgeons with a special interest in colorectal pathology.

A retrospective study was performed with a data-base created with prospective information collected about the patients (age, sex, body mass index [BMI], and American Society of Anesthesiologists [ASA] score),[23] the surgical procedures (type and duration of surgery, ileostomy, type of anastomosis and blood transfusion), radiotherapy dose, duration, and interval between radiotherapy and surgery), and the tumor (staged according to the tumor, node, metastasis system,[24] and location). Diagnostic procedure and disease stratification was performed with abdominal and pelvic computed tomographic scan, magnetic resonance imaging, and rectal ultrasonic endoscopy with biopsy. All patients with a pathology diagnosis other than adenocarcinoma, those undergoing emergency surgery, those with coexistent malignant tumor, or those who had undergone previous rectal surgery were excluded.

Patients were allocated to two different groups: group A was made up of 170 patients who were provided both chemoradiotherapy and surgery, and group B was made up of 103 patients treated

with surgery alone. Neoadjuvant chemoradiotherapy was indicated for patients whose preoperative staging revealed tumor infiltration deeper than the muscular layer (T3) or lymph nodes suspicious of metastasis (N+) and in eight patients with stage T2N0 in an effort to improve the sphincter preservation rate. All patients not fulfilling these criteria (71 of 103) as well as those with metastasis (M1) (24 of 103) were included in group B, so that systemic chemotherapy would not be delayed. Finally, patients who refused preoperative chemoradiotherapy were also assigned to group B (8 of 103). In 12 patients included in group A, we found intraoperative M1 disease. They were excluded from this study, as were patients with unresectable metastasis disease treated with preoperative chemotherapy.

Preoperative Radiotherapy

External radiotherapy techniques were delivered in two, three, and four fields according to the guidelines provided in Report 50 of the International Commission on Radiation Units and Measurements,[25] including the primary tumor and regional, mesorectal, presacral, and internal iliac (up to L5-S1) lymph nodes. Most of the patients (77 of 103) received a standard dose of 45–504 Gy in 25 fractions over 5 weeks, combined with chemotherapy based on 5-fluorouracil (5-FU) boluses during the first and last week of radiotherapy. Fifteen patients received a reduced dose because of intolerance, and 11 received a dose over 50.4 Gy. All of them underwent surgery between the fourth and sixth week after completing radiotherapy.

Surgical Procedures

All the patients underwent intestinal preparation the day before surgery, as well as intestinal decontamination with oral antibiotic therapy, antithrombotic prophylaxis with low molecular weight heparin, gastric protection with ranitidine, and intravenous antibiotic prophylaxis against anaerobes and gramnegative bacteria. The procedures used were as follows: low anterior resection with mechanical anastomosis, Miles abdominoperineal amputation, and the Hartmann procedure. A protective ileostomy was created according to the surgeon's decision, taking into account technical factors, the general health of the patient, and the use of neoadjuvant therapy with chemoradiotherapy. In all cases, information was gathered prospectively about the duration of the surgical procedure, blood loss, and intraoperative blood transfusion requirements as decided by the anesthetists.

Pathological examination of the surgical specimens was carried out by the same pathologist, who classified them according to the tumor, node, metastasis staging system. Postoperative 5-FU-based adjuvant therapy was provided to those patients in group A found at pathological examination to have persistent disease. Adjuvant therapy was also suggested for those patients belonging to group B with stage III and IV disease.

Complications

Postoperative complications were recorded as follows: 1, surgical wound complications (infection, seroma, abscess); 2, intra-abdominal abscess; 3, anastomotic leak (considered when clinical symptoms and required reoperation or interventional radiology) 4, postoperative hemorrhage (rectorrhagia and hemoperitoneum); 5, urinary disturbances (retention, infection, dysuria); 6, general complications (pulmonary, cardiovascular, catheter sepsis, thrombosis); and 7, paralytic ileus (continued nasogastric tube on the fifth postoperative day or reintroduction of the tube). Surgical

mortality was defined as mortality within the first 30 days after surgery.

Statistical Analysis

Data were collected from a computer database. Data collection was supervised by the same surgeon throughout the study. Data analysis was performed by SPSS 11.0 software (SPSS, Chicago, IL).

Categorical variables were analyzed by contingency tables and x^2 or Fisher exact probability, depending on the cases. Continuous variables were analyzed with the Student t-test. The association between independent variables and complications was analyzed with lineal logistic regression. P values below .05 were considered to be statistically significant.

RESULTS

Series Analysis

The demographic characteristics of the 273 patients are shown in Table 1. The two groups were homogeneous in age, sex, BMI, ASA, tumor location, type of surgery, blood transfusion, duration of surgery, and duration of hospitalization. Differences in tumor stage between groups were caused by the selection groups.

The rate of pT0 in patients treated with chemoradiotherapy was 15%. We found 31.5% of patients to have lymph nodes metastasis (N+), and we found positive circumferential margins in seven cases (four in group A).

Most of the patients allocated to preoperative chemoradiotherapy (group A) received a standard dose of 45–50.4 Gy, with conventional fractioning (1.8 Gy), during a 5-week period. The mean dose was 4700 cGy (range, 3696–6500 cGy). Chemotherapy with 5-FU (350 mg/m^2/day) was given in the first and last weeks of the radiation period. The average time between preoperative chemoradiotherapy and surgery was 8 days (range, 30–61 days). The mean radiotherapy duration was 36 days (range, 20–70 days).

The characteristics of the surgical procedures in both groups, with values of statistical significance, are displayed in Table 1. Thirty-five percent of patients were admitted to the intensive care unit (ICU) after surgery. The mean duration of surgery was 170 minutes (range, 70–540 minutes) in group A and 150 minutes (range, 45–330 minutes) in group B, which was not statistically significant. No statistically significant differences between the groups were found with regard to sphincter-preserving surgery (76.5% in group A vs. 75.5% in group B) or blood transfusion (16.6% in group A vs. 18.1% in group B). A total of 31.2% patients in group A underwent ileostomy, versus 8.8% in group B ($P < .001$). Other surgical procedures (cholecystectomy, hysterectomy, hernia surgery) were combined with the tumor excision in 13% of the patients in group A, versus 22.3% in group B ($P < .045$).

Complications

The complications found in both groups are listed in Table 2. Its important to note that although statistically significant differences were not found, the number of patients who experienced complications was smaller in group A (23%) than in group B (32%). However, the number of

complications was similar in both groups (43.1% vs. 44.6%).

Similar rates of surgical wound infection (8.2% vs. 7.8%), intra-abdominal abscess (4.7% vs. 4.9%), suture dehiscence (4.2% vs. 3.8%), postoperative hemorrhage (3.5% vs. 3.9%), urinary disturbances (6.5% vs. 4.9%), paralytic ileus (8.9% vs. 9.7%), and general complications (7.1% vs. 9.6%) were also found. All cases of anastomotic leak occurred in patients without an ileostomy.

The global mortality in the series was two patients (.7%), one in each group. One patient (.6%) in the group treated with chemoradiotherapy died of severe myocardial ischemia during the early postoperative period, and one patient (1%) in the group treated with surgery alone died of intra-abdominal hemorrhage.

Univariate analysis (Table 3) showed that those patients with ASA III–IV tumors included a higher number of patients with complications ($P < .001$), surgical wound infection ($P = .023$), paralytic ileus ($P = .028$), and general complications ($P < .01$) than ASA I–II tumors.

Surgical procedures lasting longer than 3 hours were also associated with a higher proportion of patients with complications ($P = .006$) and wound infections ($P < .001$). Blood transfusion during surgery was associated with a significantly higher rate of intra-abdominal abscess ($P = .004$) and anastomotic dehiscence ($P = .004$).

In the multivariate analysis, male sex, ASA III–IV score, surgery lasting longer than 180 minutes, BMI >30, the Hartmann procedure, and blood transfusion were variables significantly associated with a higher risk of complications (Table 4).

DISCUSSION

Neoadjuvant radiotherapy with or without chemotherapy has been widely used in patients diag nosed with rectal cancer to achieve better outcomes. Several controlled studies have showed a lower rate of local recurrence in those patients treated with a combination of radiotherapy and surgery.[9,19,26] However, it is not easy to assess the effect of longterm radiotherapy on early postoperative morbidity and mortality. Potential problems related to preoperative radiotherapy are perianal sepsis, delayed surgical wound healing, and a higher rate of anastomotic dehiscence,[26–28] although many authors disagree, given that the use of temporary stomas without well-defined, universal criteria makes it difficult to analyze. A comparative analysis of the available studies is difficult because of the different inclusion criteria and chemoradiotherapy modalities used and because of variations in the standardization of surgical procedures. The aim of this study was to analyze the early (30 days) postoperative morbidity and mortality in patients with rectal adenocarcinoma, comparing two groups with similar surgical procedures, with and without preoperative radiotherapy. Furthermore, we assessed the prognostic factors related to those complications.

Patients in both groups had homogenous characteristics concerning age, sex, BMI, ASA, tumor location, and type of surgical procedure. We used a long-radiotherapy protocol with treatment of 5.4 Gy provided to the tumor, as opposed to protocols of short duration, because of the benefits evidenced in downstaging. In our experience, 15% of patients treated according to this protocol had a complete response (n = 25), as assessed by pathology. Clinical staging of the tumors with the currently available tools makes it unlikely that patients with low-stage disease (T1-T2N0) would be overstaged or that patients would have distant metastasis, especially after including endoscopic

ultrasound, which has a sensitivity of >90%.[29]

It seems that the combination of both adjuvant therapies increases the rate of complications associated with therapeutic toxicity compared with radiotherapy alone. Although this fact could be related to the synergistic effect of the two modalities, the correlation between neoadjuvant toxicity and postoperative complications has not been clearly determined.[31,32]

We have found a dose- and time-dependent correlation, although it is not statistically significant, between radiation and some postoperative complications. When analyzed individually, those patients in group A with general complications, wound infection, intra-abdominal abscesses, and anastomotic leak had received a higher mean dose of radiotherapy and had experienced a longer time interval between neoadjuvant therapy and surgery.

In our own experience, and in agreement with other published studies,[14,15,31–33] we consider that preoperative chemoradiotherapy does not increase either the number of early postoperative complications or the rate of surgical mortality. We should be cautious with these results because ours is not a randomized, double-blind study. However, taking into account the long experience of our team, the standardization of therapy, and the homogeneity of both groups analyzed, we believe that the results obtained constitute valid information for the study of complications.

The proportion of patients with complications in the group that received chemoradiation (23%) is lower than that in the group that did not receive chemoradiation (32%). However, the number of complications was similar for both groups (43.1% vs. 44.6%). These results are in agreement with those published by other authors.[14,15,34]

As described in other published studies,[26,34,35] We also found a higher rate of wound infection in the chemoradiotherapy group (8.8%), mainly as a result of infection of the perianal wound in those patients undergoing rectal amputation. However, we did not find relevant differences in the incidence of intraabdominal abscesses (4.7%) and anastomotic dehiscence (4.2%). These results are in agreement with those described by Enker et al.,[36] who concluded that preoperative chemoradiotherapy increases the time of surgery, blood loss, and formation of pelvic abscesses but does not increase anastomotic dehiscence or duration of hospitalization.

The literature shows a percentage of global anastomotic leak ranging from 0% to 17.4%,[14,15,37–42] without any differences found between groups in many of the studies.[14,15,27,34,41,43] However, the results are difficult to compare because of the heterogeneity of the studies and the different meanings assigned to the term leak. The use of temporary stomas has been generally suggested for tumors located <6 cm from the anal verge because of the higher risk of leakage. There is probably a direct correlation between anastomotic leakage and lack of stoma.[15,41,43] Peeters et al.[41] associated the lack of ileostomy and pelvic drainage to a higher likelihood of anastomotic leak.

Temporary protective ileostomy was performed when faced with technical difficulties during the anastomosis, such as lack of watertightness and incomplete donut. However, some studies have not demonstrated a correlation with anastomotic leak.[40] In our hospital, the use of preoperative chemoradiotherapy was a further factor for prescribing temporary diverting ileostomy. We observed a slightly higher mean radiotherapy dose (4995 vs. 4700 cGy) among those patients in the group treated with radiotherapy in whom an anastomotic leak was detected.

Mortality in the first 30 days after surgery was .6% for group A and 1% for group B. These results were similar to those described by Enker et al.,[39] Heald et al.,[44] and Read et al.,[42] and better than those published in other series.[45] An important factor for this may be the exclusion of patients undergoing emergency surgery, which is often associated with an increase in morbidity and mortality. This same study concludes that the risk of postoperative mortality is associated with the

technique used in the preoperative radiotherapy; it is higher when two fields are used. The Swiss study[30] states that postoperative mortality is associated with the total dose of radiotherapy, the time interval between radiotherapy and surgery, and the type of radiotherapy administered. We were unable to study these risk factors because of the lack of statistical power of our study, which was related to a low incidence of death.

By means of multivariate analysis, we found the following independent prognostic factors for the development of postoperative complications: sex, ASA score, BMI, blood erythrocyte transfusion during the surgical procedure, Hartmann procedure, and duration of surgery. We conclude from our results that ASA III–IV score and a lengthy duration of surgery (>3 hours) are directly associated with several postoperative complications. Thus, classical preoperative and patient-dependent risk factors and intraoperative and surgeon-dependent factors are associated with postoperative morbidity and mortality. On the other hand, neoadjuvant therapy is not associated with postoperative complications.

In summary, the use of neoadjuvant chemoradiotherapy in patients with rectal cancer is not associated with a higher rate of early postoperative complications in general and with anastomotic leak in particular. The patient's preoperative condition (patient state) as defined by ASA score III–IV and a lengthy duration of surgery are independent prognostic factors for the development of surgical complications.

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TABLES

TABLE 1. Patient, tumor, and surgical characteristics

Characteristic	Group A (n) (n = 170)	%	Group B (n) (n = 103)	%	Total (n) v	%	P value
Age, y							
<51	37	21.7	13	12.6	50	18.3	.274
51–60	46	27.1	30	29.1	76	27.8	
61–70	60	35.3	39	37.8	99	36.2	
>70	27	15.9	21	20.4	48	17.5	
Sex							
Male	116	68.2	68	66	184	67.4	.705
Female	54	31.7	35	34	89	32.6	
BMI (kg/m2) <25	55	32.3	36	34.9	91	33.3	.737
25–30	89	52.3	49	47.5	138	50.5	
>30	26	15.3	18	17.4	44	16.1	
ASA score							
I–II	118	69.4	76	73.8	194	71.1	.440
III–IV	52	30.6	27	26.2	79	28.9	
Distance from anal verge, cm <6	61	35.9	31	30.1	92	33.7	.513
6–11	67	39.4	41	39.8	108	39.6	
12–16	42	24.7	31	30.1	73	26.7	

TNM stage							
T0	25	14.7	–	–	25	9.1	<.001
T1	13	7.6	8	7.9	21	7.8	
T2	44	25.8	43	41.6	87	31.8	
T3	80	47.1	42	40.6	122	44.7	
T4	8	4.8	10	9.9	18	6.6	
N0	116	68.2	71	68.9	187	69.2	.449
N1	42	24.7	21	20.3	63	23.3	
N2	12	7.1	11	10.6	23	8.4	
M0	158	92.9	79	76.7	237	87	.001
M1	12	7	24	23.3	36	13	
Operation type							
LAR	121	70.6	80	76.7	199	72.9	.308
APR	40	23.5	17	15.5	56	20.5	
Hartmann	9	5.3	6	5.8	15	5.5	
Mean (range) duration (min) of procedure	170 (70–540)	60.8	150 (45–330)	51.7	–	–	.405
Mean stay (days)	10 (5–25)	–	10 (3–45)		–	10 (3–45)	.287
Diverting stoma	46	27.1	7	6.8	53	19.4	<.001
Associated operation	22	12.9	23	22.3	45	16.4	.045
Blood transfusion	28	16.4	17	16.5	45	16.4	.754

BMI, body mass index; ASA, American Society of Anesthesiologists; TNM, tumor, node, metastasis system; LAR, low anterior resection; APR, abdominoperineal resection.

TABLE 2. Postoperative complications

Complication	Group A, n (%)	Group B, n (%)	Total, n (%)	P value
No. of patients with complication	39 (22.9)	33 (32.0)	72 (26.4)	.098
Wound infection	15 (8.2)	7 (7.8)	22 (8.1)	.890
Abdominal abscess	8 (4.7)	5 (4.9)	13 (4.8)	.955
Anastomotic leak	5 (4.2)	3 (3.8)	8 (3.6)	.797
Hemorrhage	7 (3.5)	4 (3.9)	11 (3.7)	.880
Urinary complications	12 (6.5)	5 (4.9)	17 (5.9)	.582
Postoperative ileus	15 (8.9)	10 (9.7)	25 (9.2)	.818
Other	13 (7.1)	10 (9.6)	23 (8.1)	.390
Mortality	1 (.6)	1 (1)	2 (.7)	.719

TABLE 3. Univariate analysis of complications

Variable	Complication	No complication	P value
No. of patients with complication			
ASA I–II	40	154	<.001
ASA III–IV	32	47	
Operation duration <180 min	32	129	.006
Operation duration >180 min	35	64	
Wound infection			

ASA I–II	11	183	.023
ASA III–IV	11	68	
Operation duration <180 min	4	157	<.001
Operation duration >180 min	15	84	
Abdominoperineal resection	11	45	.002
BMI >30 kg/m^2	6	30	<.001
Postoperative ileus			
ASA I–II	32	129	.028
ASA III–IV	35	64	
Male	22	161	.004
Abdominal abscess			
Hartmann	3	12	.029
Blood transfusion	6	39	.004
Anastomotic leak			
Blood transfusion	4	41	.004
General complications			
ASA I–II	11	183	<.0
ASA III–IV	11	68	01

ASA, American Society of Anesthesiologists; BMI, body mass index.

TABLE 4. Multivariate analysis showing factors associated with postoperative complications in 273 patients[a]

Variable	RR	95% CI	P value
ASA III–IV	2.43	1.34–4.42	.030
Operation duration >180 min	2.13	1.20–3.79	.010
Wound infection			
ASA III–IV	2.73	1.05–7.13	.039
Operation duration >180 min	6.66	2.07–21.40	.001
BMI >30 kg/m^2	5.84	1.11–30.70	.037
Abdominal abscess			
Hartmann	9.75	1.94–48.92	.008
Blood transfusion	5.04	1.52–16.62	.008
Postoperative ileus			
Male	3.85	1.10–13.41	.034
ASA III–IV	2.32	.90–5.48	.053

RR, relative risk; 95% CI, 95% confidence interval; ASA, American Society of Anesthesiologists; BMI, body mass index.

[a] No independent prognostic factors were found for the complications of anastomotic leak and hemorrhage.