The Long-Term Effect of Adjuvant Postoperative Chemoradiotherapy for Rectal Carcinoma on Bowel Function

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Objective

The authors assessed the long-term effect of postoperative chemoradiotherapy on bowel function.

Summary Background Data

Adjuvant postoperative radiation therapy, often combined with chemotherapy, is being used increasingly often for rectal carcinoma. However, the long-term effect of this treatment on bowel function has not been investigated.

Methods

The records were reviewed of all patients undergoing anterior resection for rectal carcinoma 2 to 5 years previously. During this period, patients with Astler-Coller stage B2 or C tumors generally were given postoperative radiation therapy with chemotherapy, whereas those with earlier stage tumors were not. To minimize possible confounding factors that may have been more common in the group receiving chemoradiotherapy and that may affect bowel function, extensive exclusion criteria were used, such as invasion of contiguous organs, local or distant metastases, use of a dysfunctioning stoma, and anastomotic or pelvic complications. One hundred remaining patients were suitable for inclusion in the study and participated in a telephone questionnaire; 41 patients had postoperative chemoradiotherapy, and 59 did not.

Results

The two groups were well matched for sex, level of anastomosis, and length of follow-up, although the group receiving chemoradiotherapy was slightly younger. The group that had chemoradiotherapy had more bowel movements per day than the group that did not have radiation therapy (median 7 vs. median 2, p < 0.001); the former group had "clustering" of bowel movements more often (42% vs. 3%, p < 0.001), had nighttime movements more often (46% vs. 14%, p < 0.001), had occasional or frequent incontinence more often (39% and 17% vs. 7% and 0%, p < 0.001), wore a pad more often (41% vs. 10%, p < 0.001), and were unable to defer defecation for more than 15 minutes more often (78% vs. 19%, p < 0.001). The group that had chemoradiotherapy also had stool of liquid consistency, used antidiarrheal medications, had perianal skin irritation, were unable to differentiate stool from gas, and needed to defecate again within 30 minutes of a movement significantly more often than the group that did not receive chemoradiotherapy.

Conclusion

Adjuvant postoperative chemoradiotherapy for rectal carcinoma has a major long-term detrimental effect on bowel function.

Successful management of rectal carcinoma began in the early twentieth century with the introduction of abdominoperineal resection of the rectum, in which a permanent colostomy is created.[1] Later, in an effort to improve postoperative quality of life by re-establishing intestinal continuity, anterior resection was introduced.[2] With the subsequent introduction of circular stapling devices, tumors of the lower rectum could be excised reliably with re-establishment of intestinal continuity.[3,4] There is no difference in recurrence or survival rates between abdominoperineal excision and anterior resection when there is an adequate distal margin.[5-7] Moreover, even in very low anterior resections, acceptable bowel function usually is achieved, and quality of life is superior to that after abdominoperineal excision.[8-9]

After surgical treatment alone for rectal carcinoma, both local recurrence and distant metastases are significant problems and, in an attempt to decrease these, a number of forms of adjuvant therapy have been investigated. Radiation therapy, given preoperatively or postoperatively, has been found to decrease local recurrence rates, but it has not been shown to improve survival.[10] In patients with tumors penetrating the muscular wall or those with involved lymph nodes, the combination of adjuvant postoperative radiation therapy and 5-fluorouracil (5-FU) has been compared with radiation alone and has been shown to improve survival and further decrease local recurrence.[11-13] While the short-term toxicity of radiation therapy (+/- chemotherapy) has been examined in previous trials, assessment of long-term toxicity either has not been noted or has concentrated on factors such as small bowel obstruction.[11-18] The objective of this study was to assess the long-term effect of adjuvant postoperative radiation therapy on bowel function. In the absence of a prospective study with a no-treatment arm, two similar groups of patients undergoing anterior resection are compared.

PATIENTS AND METHODS

Patient Selection

The records of all patients undergoing anterior resection for primary rectal adenocarcinoma at the Mayo

Clinic in the 3-year period preceding July 1991 were reviewed. This ensured a minimal period of 2 years between the date of operation and the current follow-up. Cases of colo-anal anastomoses sutured per anum were not reviewed. There were 222 anterior resections.

The two groups of patients could not be matched for pathologic stage because only patients with modified Astler-Coller stage B2 or C lesions were advised to undergo adjuvant chemoradiotherapy during the study period. However, the technique of anterior resection for rectal carcinomas that are not invading or adherent to adjacent organs is the same, regardless of the pathologic stage. Indeed, the stage usually is not known until the excised specimen is examined pathologically for depth of invasion and lymph node status. Patients with tumors that were found at operation to be invading or adherent to adjacent structures were excluded because the dissection in such cases may be more extensive, which may influence postoperative bowel function, and these patients are more likely to undergo adjuvant therapy. Additionally, to limit other possible confounding factors that may influence bowel function, some of which may be present in different proportions of the group receiving chemoradiotherapy and the group not receiving radiation, the exclusion criteria outlined in Table 1 were used. (In Table 1, only one exclusion criteria is noted per patient, the one first noted in the chart review. Thus, if a patient had a diverting stoma and later developed metastases, they were excluded first because of the diverting stoma.) There were 109 remaining patients, 66 of whom had not undergone postoperative chemoradiotherapy, and 43 of

Table 1. PATIENTS EXCLUDED FROM STUDY

Exclusion Criteria	No.
Previous or subsequent pelvic carcinoma	4
Previous or subsequent pelvic surgery	5
Preoperative or intraoperative radiation therapy	5
Metastatic disease at initial operation	31
Invasion of contiguous organs	4
Formation of colonic pouch	1
Temporary diverting stoma	22
Anastomotic leak	2
Pelvic abscess/fistula	5
Development of metastatic disease or local recurrence	11
Death since operation	23
Total	113

whom had undergone such treatment. However, 9 patients could not participate in telephone interviews (8 could not be contacted and 1 had dementia), so the final number of patients in the study was 100; 59 patients comprised the group not receiving radiation and 41 comprised the group receiving chemoradiotherapy.

Adjuvant Therapy

All 41 patients in the group receiving chemoradiotherapy had external beam radiation therapy. Thirty-six received between 50 and 54 Gy, three patients received a greater dose, and two received less because of severe side effects. Thirty-two patients underwent radiation therapy at the Mayo Clinic. These 32 and 5 of the patients treated elsewhere were treated by methods described previously;[11] 4 patients were treated with modifications of this method. Chemotherapy was administered to all 41 patients in the radiation group. Thirty-five received 5-FU alone, four received 5-FU plus levamisole, one received 5-FU plus citrovorum factor, and one patient received 5-FU plus methyl-CCNU. In the group not receiving radiation therapy, two patients received 5-FU, and two received 5-FU plus levamisole.

Interview

The telephone interviews were performed by the same medical practitioner (C.K.) who had not participated in the patients' care. All interviews were conducted in a standardized manner, with the questions asked in the same order, using the same wording. Because of the nature of the interview, it was not possible to blind the interviewer to the treatment of the patients. Telephone interview was chosen as the method of data collection because it was considered that overall compliance with a postal questionnaire would not be as high, and individual compliance may have been influenced by postoperative treatment and bowel function.

Patients were asked about the number of stools passed during the day and at night, and about incontinence during the day and night. Incontinence was graded as nil, occasional (≤1 × once per week), or frequent (>1 × per week). They were asked if they were able to defer defecation for more than 15 minutes after the first urge to defecate, and whether they frequently needed to defecate again within 30 minutes of a bowel movement. In addition, questions were asked about the need to wear a pad, the presence of perianal skin irritation, the ability to reliably distinguish between flatus and feces, the normal consistency of the stool (liquid, semi-solid, or solid), the presence of bleeding, and the use of antidiarrheal medications. Patients were asked if their bowel function was

Table 2. COMPARISON OF PARAMETERS OF THE TWO GROUPS

	Non-Radiation Group	Chemo-radiotherapy Group	p Value
Mean age (range)	66.6 (46–85)	62.6 (44–81)	0.054
Male:female	33:26	27:14	0.407
Mean calculated level of anastomosis (range)	7.8 cm (3–15)	7.9 cm (3–15)	0.637
Stapled vs. handsewn	34:25	28:13	0.303
Mean interval from operation to interview (range)	40 mo (24–60)	42 mo (25–61)	0.364

significantly different from their preoperative function, and finally, if they were considering undergoing an operation to create a permanent colostomy, because of poor bowel function.

Data Analysis

All medical records were available for review. The level of the anastomosis above the anal verge was noted only in a minority of cases. So that the level of the anastomoses could be compared in both groups, the level was calculated by subtracting the distal resection margin, measured in the fresh pathologic specimen, from the level of the tumor noted on preoperative proctoscopic examination. The records were insufficient to calculate the level of anastomosis in six patients in the nonradiation group and one patient in the radiation group receiving.

Fisher's exact test was used to compare proportions of events in the two groups when there were two possible outcomes. When there were more than two outcomes, chi square analysis was used. The exact Wilcoxon test was used to compare the age, level of anastomosis, and number of bowel movements per day in the two groups, and for examining the effect of the patient's sex on the number of movements per day and fecal incontinence. After comparison of the two groups, Spearman's rank correlation coefficient was used to examine the association between the number of bowel movements per day and incontinence, and the age, level of anastomosis, and the length of follow-up.

RESULTS

The groups were well matched for sex, calculated level of anastomosis, method of anastomosis, and length of follow-up, although there was a small difference in the ages (Table 2). The Astler-Coller stage of the tumors in

Table 3. SUMMARY OF BOWEL FUNCTION IN THE TWO GROUPS

	Non-Radiation Group (59 patients)	Chemoradiotherapy Group (41 patients)	p Value
No. of bowel movements/day			
Median (range)	2 (1–7)	7 (1–20)	<0.001
≤4	83%	22%	
"Clustering"	3%	42%	
≥5	14%	37%	
Awoken at night for movement	14%	46%	<0.001
Incontinence			<0.001
None	93%	44%	
Occasional	7%	39%	
Frequent	0%	17%	
Wear a pad	10%	41%	<0.001
Perianal skin irritation	12%	41%	<0.001
Regularly use Lomotil ±/− Imodium	5%	58%	<0.001
Unable to differentiate stool from gas	15%	39%	0.009
Liquid consistency (sometimes or always)	5%	29%	0.001
Unable to defer defecation >15 min	19%	78%	<0.001
Need to defecate again within 30 min	37%	88%	<0.001
Bowel function different to preoperative	61%	93%	0.001

the group not receiving chemoradiotherapy was A in 11 cases, B1 in 34 cases, B2 in 7 cases, and C in 7 cases. In the group receiving chemoradiotherapy, there were 17 stage B2 tumors and 24 stage C tumors ($p < 0.001$). Eighteen patients reported symptoms of radiation-proctitis during their course of radiation therapy.

The results of the questionnaire are summarized in Table 3. In the nonradiation group, 49 of the 59 patients (83%) reported that they had ≤4 bowel movements per day, whereas 8 (14%) had ≥5 bowel movements per day, and 2 (3%) reported "clustering," with few or no bowel movements on some days and ≥5 bowel movements on other days. However, in the group receiving chemotherapy, only 9 of 41 patients (22%) had ≤4 bowel movements per day, whereas 15 (37%) had ≥5 bowel movements per day and 17 (42%) reported clustering ($p < 0.001$). The phenomenon of clustering was an unexpected finding, and patients found it impossible to state an average number of stools per day. They frequently volunteered that they had to adjust their lifestyle in anticipation of the possibility of the need to pass frequent bowel movements. The median number of bowel movements per day (in those with clustering, the reported number of bowel movements on days when there were bowel movements was used) was 2 (range 1–7) in the nonradiation group and 7 (range 1–20) in the group receiving chemoradiotherapy ($p < 0.001$) (Fig. 1). Even if those with clustering are excluded, the median number of bowel movements per day was 2 (range 1–6) and 6 (range 1–12), respectively ($p < 0.001$). In the nonradiation group, 8 patients (14%) regularly needed to wake at

night to pass a bowel movement, compared with 19 (46%) of the group undergoing chemoradiotherapy ($p < 0.001$).

Fifty-five patients (93%) in the nonradiation group reported normal continence, whereas four (7%) reported occasional soiling (three during daytime and one at nighttime), and none had frequent incontinence. In the group receiving chemoradiotherapy, only 18 (44%) reported normal continence ($p < 0.001$). Sixteen (39%) reported occasional incontinence (ten during daytime, one at nighttime, and five during both), whereas seven (17%) reported frequent incontinence (four during daytime, one at nighttime, and two during both). Six patients (10%) in the group not receiving radiation therapy wore a pad compared with 17 (41%) in the group receiving chemoradiotherapy ($p < 0.001$). Seven (12%) of the nonradiation group suffered perianal skin irritation, compared with 17 (41%) of the chemoradiotherapy group ($p < 0.001$). Three patients (5%) in the nonradiation group regularly used Imodium or Lomotil, compared with 23 (58%) of the chemoradiotherapy group ($p < 0.001$). Nine patients (15%) in the nonradiation group were unable to differentiate stool from gas compared with 14 (39%) of the chemoradiotherapy group ($p < 0.009$).

The consistency of the feces was occasionally liquid in three patients (5%) in the nonradiation group. In the group receiving chemoradiotherapy, it was liquid sometimes in six patients (15%) and always liquid in another six (15%) ($p = 0.001$). Eleven patients (19%) in the nonradiation group reported that they were unable to hold a bowel movement for more than 15 minutes after the first
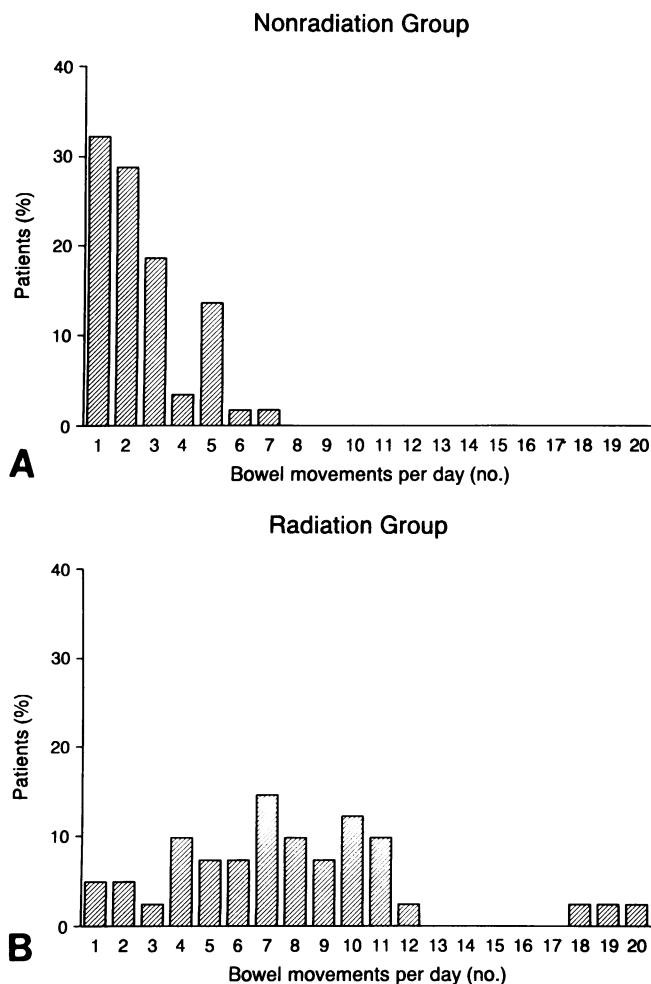
Nonradiation Group

A Bowel movements per day (no.)

Radiation Group

B Bowel movements per day (no.)

Figure 1. Histograms comparing the number of bowel movements per day in the nonradiation and radiation groups.

urge to defecate, compared with 32 (78%) of the chemoradiotherapy group (p < 0.001). Twenty-two patients (37%) in the nonradiation group usually needed to defecate again within 30 minutes of a bowel movement, whereas 36 patients (88%) in the group receiving chemoradiotherapy reported this (p < 0.001).

When asked if their present bowel function was significantly different from their preoperative function, 36 (61%) of the nonradiation group said that there was a significant difference, compared with 38 (93%) of the chemoradiotherapy group (p = 0.001). No patients complained of bleeding. Two patients, both in the group receiving chemoradiotherapy, were strongly considering conversion to a permanent colostomy.

Univariate analysis of the effect of age, sex, level of anastomosis, and length of follow-up (range 2–5 years) on incontinence and the number of bowel movements per day, in both groups, revealed no significant effect from these four factors.

DISCUSSION

The findings of this study demonstrate that postoperative chemoradiotherapy has a major detrimental effect on long-term bowel function. This was not a prospective randomized study, however, it is unlikely that confounding factors could account for the markedly different results of the two study groups. Although this clinical effect of adjuvant chemoradiotherapy has not been documented previously, there has been prior work on bowel function after anterior resection and the effect of radiation on anorectal physiology. It is worth examining this previous work in light of the findings of the present study.

In the early postoperative period after anterior resection, bowel function often is compromised, with frequent bowel movements and fecal incontinence. Bowel function improves over the ensuing 1 to 2 years, and this improvement correlates well with increasing capacitance of the "neorectum."[19-21] Because of this early improvement in function, the current study only examined long-term bowel function more than 2 years after anterior resection. The current study did not find a significant correlation between the level of the anastomosis and postoperative stool frequency or incontinence. Previous investigations have demonstrated such a correlation, with lower anastomoses being associated with greater stool frequency and more incontinence.[22-24] This apparent contradiction may be partly due to the selection criteria used in the present study, which were not used in the previous investigations. Short-term follow-up, during which the greatest deterioration in bowel function occurs, was excluded. Also excluded were patients who had sutured colo-anal anastomoses. Furthermore, patients who had extensive resections, dysfunctioning stomas, or clinically significant anastomotic leaks were excluded. In these groups, very low anastomoses may be more common, and postoperative function may be worse.

One previous investigation of ten men with symptoms of radiation damage 2 to 6 years after radiation therapy for prostatic carcinoma found that the resting anal pressure and anal sphincter length were decreased significantly, when compared with age and sex matched controls.[25] There also was a significant reduction in rectal capacity and compliance.[26] Histologic specimens from eight other patients who had undergone proctectomies for radiation injury also were examined.[27] The most outstanding features were hypertrophy of the muscularis mucosae and the muscularis propria, with degeneration of both Meissner's and Auerbach's plexi. In addition to these effects, damage to the tissues surrounding the anus and rectum may contribute to the long-term changes in

bowel function. Magnetic resonance imaging of the pelvis after radiation therapy has demonstrated alterations in the signal from striated muscle, with thickening of the perirectal fascia and presacral space.[28] The physiologic and pathologic changes probably evolve over a prolonged period. In a study of 20 patients who underwent preoperative radiation for rectal carcinoma, the anal sphincter pressures had not decreased when measured 4 weeks after the radiation was completed.[29] Furthermore, histologic examination of the excised specimens revealed only minimal changes. A recent abstract reported nine patients who underwent postoperative radiation therapy after anterior resection.[30] Although the selection criteria for this study are not stated, the neorectal capacity and compliance were less in these patients than in patients who had not undergone radiation therapy.

It is likely that the clinical effects of postoperative radiation therapy are partly the result of decreased rectal capacity and compliance. However, changes in rectal motor and sensory function and changes to the surrounding soft tissues may contribute. Changes in anal sphincter function may be reliant on the radiation fields employed. In addition, small bowel radiation damage may be relevant in explaining why nearly one third of the patients in the current study reported a feces of liquid consistency.

Although preoperative radiation therapy may cause less long-term bowel dysfunction than postoperative therapy, because the neorectum is not irradiated, preoperative radiation still will effect the surrounding tissues so that there will be some effect on bowel function. A study of preoperative intraluminal radiotherapy found that those given high-dose preoperative radiotherapy subsequently had decreased postoperative anal sphincter pressures and neorectal capacity and worse bowel function than those receiving low-dose or no preoperative radiotherapy.[31] The effects of conventional external beam preoperative radiotherapy on long-term bowel function have not been documented fully. One implication of the current study is the need to investigate measures that may prevent radiation damage to the rectum or neorectum. For example, one study of patients undergoing radiation therapy for prostate or bladder carcinoma demonstrated that sucralfate decreased the incidence of bowel dysfunction.[32] Finally, in this study, all patients in the group receiving radiation also received adjuvant chemotherapy, and the added influence of this on the long-term bowel function is unknown.

The only adjuvant therapy that has been shown convincingly to improve survival in prospective trials in patients with rectal carcinoma is the combination of postoperative radiation therapy and chemotherapy.[11–13] This treatment results in a significant long-term detrimental effect on bowel function. Patients should be informed of this effect. Alternative forms of treatment, such as preoperative radiation or chemotherapy, may prove comparable in terms of local recurrence and survival, but have less long-term morbidity. A recently developed stage III intergroup trial, sponsored by the Radiation Therapy Oncology Group, comparing preoperative and postoperative adjuvant chemoradiotherapy should provide more definitive information in this regard. In uncontrolled reports, surgery alone, with total mesorectal excision, has been associated with low local recurrence rates, although short-term morbidity is significant.[33] It would be ideal if future studies of the treatment of rectal carcinoma compared survival, local recurrence, and both short-term and long-term morbidity.

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