Hypothesis: Pelvic irradiation adversely affects anal sphincter function after proctectomy with coloanal anastomosis for low rectal and middle rectal (≤10 cm from the anal verge) tumors.

Design: Case-control study.

Setting: Private, tertiary care referral center.


Interventions: Anal manometric data were prospectively collected at the time of initial diagnosis and before ileostomy closure.

Main Outcome Measures: Mean and maximum resting pressures (RPs) and squeeze pressures, threshold volume for sensation, and maximal tolerable volume.

Results: Twenty-three patients in the surgery group and 19 in the chemoradiotherapy group were considered for analysis; 15 patients had preoperative radiotherapy and 4 had postoperative radiotherapy. At the time of ileostomy closure, RPs were significantly lower in the chemoradiotherapy group than in the surgery group (32.7±17 vs 45.3±18 mm Hg; P = .03). Squeeze pressures were not significantly different between the surgery and chemoradiotherapy groups (108.7±56.7 vs 102.0±52.6 mm Hg; P = .69). The ratios of postresection to preresection RPs were also significantly lower in the chemoradiotherapy group (0.49±0.29) than in the surgery group (0.76±0.22) (P = .005). Eight to 12 weeks after proctectomy with coloanal anastomosis, a 24% decrease in RP was noted in the surgery group. The addition of adjuvant pelvic irradiation decreased RP by another 27%.

Conclusion: Adequate shielding of the anal sphincter should be performed for low rectal cancers whenever a sphincter-preserving procedure is considered.

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In April 1990, a panel of experts under the auspices of the National Cancer Institute recommended adjuvant therapy consisting of radiotherapy, chemotherapy, or both for all patients with stages II and III rectal cancer. During the last 2 decades, the technical feasibility of proctectomy with coloanal anastomosis (PCAA) has increased with the advent of circular stapling devices and the knowledge that distal margins of resection of 2 cm are adequate. Thus, it is expected that an increasing number of patients with rectal cancer will receive a combination of sphincter-preserving surgery and pelvic radiation. However, few data are currently available to quantitatively assess the effects of irradiation on anorectal function.

Currently, management of stages II and III rectal cancer includes preoperative or postoperative radiotherapy to the pelvis with continuous infusion of fluorouracil. A total dose of 50.4 Gy is delivered in 28 fractions over 5½ weeks (1.8 Gy/fraction). The modalities of pelvic irradiation and the inclusion or not of the anal canal are important considerations because there are dose-related toxic effects on normal tissues. Moreover, irradiation-induced fibrosis and damage to the vascular endothelial cells is known to progress over time.

The Swedish Rectal Cancer Trial Group reported the functional results of their study, in which patients with rectal cancer were randomly assigned to receive surgery alone or preoperative irradiation (25 Gy delivered in 5 fractions in 1 week) followed by surgery. A standardized protocol was implemented, with inclusion of the anal canal in all cases, including tumors located in the upper rectum. It was demonstrated that 30% of
PATIENTS AND METHODS

All patients who underwent a PCAA for rectal adenocarcinoma between January 1, 1994, and October 31, 1999, were entered into a prospective database. Two surgeons (S.W. and E.W.) routinely performed anal manometry at the time of diagnosis and before ileostomy closure. Initial clinical assessment included rigid proctoscopy and endorectal ultrasound to assess the distance of the cancer from the anal verge and its preoperative staging. These assessments provided the base for subsequent decisions regarding adjuvant chemoradiotherapy. Tumors 6 to 10 cm from the anal verge were defined as middle rectal cancers, and those within 5 cm of the anal verge were defined as low rectal cancers. After surgery, distance of the anastomosis from the dentate line was confirmed by follow-up colonoscopy, usually performed 1 year after the initial procedure.

MANOMETRY

Manometric evaluation of anal sphincter function was performed in our Physiology Laboratory using a technique described previously. A station pull-through technique was used, with a polypropylene flexible catheter comprising 4 radial ports (Arndorfer Inc, Greendale, Wis). An 8-channel hydraulic capillary infusion system was used with Medex transducers (Medex Inc, Hilliard, Ohio). Mechanical pressures are transmitted to a PC polygraph HR (Synectics Medical Inc, Irving, Tex), and the resulting electrical impulses were displayed on an IBM-compatible computer using Polygram 2.02 for Windows Base Module software and Polygram 2.0 for Windows Anorectal Manometry Analysis Module (Medtronics Inc, Minneapolis, Minn). With the patient in the left lateral decubitus position, the catheter is inserted to 6 cm, and the measurements are repeated at a further 5 stations separated by 1-cm intervals as the catheter is progressively moved caudad. The RPs and SPs over the entire length of the anal canal can be measured, and the mean pressures over the high-pressure zone can be calculated.

SURGERY

A standardized procedure for PCAA was realized in which the level of transection of the distal rectum was determined by the total mesorectal excision rather than by the height of the tumor. Thus, all patients had a double-stapled anastomosis constructed at the level of the surgical anal canal according to a previously described technique. Complete mobilization of the rectum with sharp dissection in the plane anterior to Waldeyer fascia was carried distally to the level of the levator muscles. Transection of the distal rectum at the level of the dentate line with a 30-mm linear stapler was performed to achieve at least a 2-cm distal free margin. A coloanal anastomosis was constructed after transanal insertion of a 28-mm circular stapler. If technically possible, a 6-cm colonic J-pouch was the preferred method for reservoir reconstruction. Diverting loop ileostomy was routinely performed, and closure was performed 8 to 12 weeks after the initial procedure.

CHEMORADIOThERAPy

The preferred mode of administration of adjuvant radiation in our institution is preoperative delivery of 45 Gy in 25 fractions over 5 to 6 weeks (1.8 Gy/fraction), followed by a boost to the primary tumor bed to a total dose of 50.4 Gy. Typically, a 4-field technique was used; the superior border was to the L5/S1 junction, and the lower limit for a PCAA was the inferior border of the ischial tuberosity. Thus, the anal canal was included in all cases within the field of irradiation. The lateral borders extended 1.5 cm beyond the bony pelvis, and the posterior border encompassed the entire sacrum. For patients who received adjuvant treatment in other institutions, the radiotherapist was contacted or the abdominal films were reviewed to confirm the dose and radiation volume. Five weeks after completion of radiotherapy, the patient was reevaluated, with special attention directed toward distal tumors, where the possibility to perform a sphincter-preserving procedure had been questionable. Surgery was routinely scheduled 6 weeks after termination of radiotherapy. The chemotherapy regimen included continuous infusion of fluorouracil at a dose of 250 mg/m² per day.

SAMPLE SIZE AND STATISTICAL ANALYSIS

It was estimated that compared with the surgery group, a 25% reduction in RP or SP in the chemoradiotherapy group would be clinically relevant. According to a previous study with identical design, we postulated that the mean±SD RP in the control group will be close to 46±12 mm Hg. To detect a 25% reduction in RP with a power of 90% and a P=.05, it was calculated that a total of 44 patients (22 in each group) would be required. Statistical analyses were undertaken using SAS statistical software (SAS Institute Inc, Cary, NC) on a UNIX system. Quantitative data were expressed as mean±SD. Groups comparisons were made using Fisher exact tests or t tests for continuous variables. To further define our analysis, paired values (before and after irradiation) were compared for each patient using a paired t test for the previously mentioned variables. All reported probability values are for 2-sided tests. Statistical significance was defined as α<.05.

irradiated patients had some degree of bowel dysfunction compared with 10% in the surgery alone group. The most frequently reported symptoms included incontinence for loose stools and urgency. It is generally recognized that adjuvant radiotherapy is a major determinant of poor bowel function after restorative proctectomy or low anterior resection. The Mayo Clinic group observed that patients who received adjuvant chemoradiation had significantly more frequent bowel movements, clustering, and incontinence. In that study, most patients were irradiated after surgery, and it was considered that poor function might in part be related to decreased capacity and compliance of the neorectum.

The quantitative evidence that pelvic irradiation affects anorectal function is scarce in patients with rectal cancer but more firmly established in patients treated for anal canal malignant neoplasms. Yeoh et al studied the anorectal function of 35 patients with prostate carcinoma irradiated with dose regimens (35 Gy in 20 fractions over 4 weeks) similar to those commonly recommended for rectal carcinoma. Four to 6 weeks after completion of radiotherapy, resting pressures (RPs) and...
Table 1

Preoperative Clinical and Manometric Characteristics of the Surgery and Chemoradiotherapy Groups

<table>
<thead>
<tr>
<th></th>
<th>Surgery Group (n = 23)</th>
<th>Chemoradiotherapy Group (n = 19)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, M/F</td>
<td>16/7</td>
<td>16/3</td>
<td>.30†</td>
</tr>
<tr>
<td>Age, mean ± SD, y</td>
<td>66 ± 12</td>
<td>68 ± 9</td>
<td>.59‡</td>
</tr>
<tr>
<td>Tumor stage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>6</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>11</td>
<td>11</td>
<td>.23†</td>
</tr>
<tr>
<td>III</td>
<td>6</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Location of tumor</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lower rectum</td>
<td>9</td>
<td>12</td>
<td>.12†</td>
</tr>
<tr>
<td>Middle rectum</td>
<td>14</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Level of anastomosis, cm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>11</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>7</td>
<td>6</td>
<td>.59‡</td>
</tr>
<tr>
<td>3</td>
<td>5</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Resting pressure, mean ± SD, mm Hg</td>
<td>57.1 ± 16.1</td>
<td>70.6 ± 20.9</td>
<td>.06§</td>
</tr>
<tr>
<td>Maximum resting pressure, mean ± SD, mm Hg</td>
<td>83.8 ± 25.6</td>
<td>94.8 ± 26.7</td>
<td>.26§</td>
</tr>
<tr>
<td>Squeeze pressure, mean ± SD, mm Hg</td>
<td>104.6 ± 51.9</td>
<td>124.8 ± 111.0</td>
<td>.21‡</td>
</tr>
<tr>
<td>Maximum squeeze pressure, mean ± SD, mm Hg</td>
<td>150.6 ± 74.8</td>
<td>187.5 ± 121.8</td>
<td>.30‡</td>
</tr>
</tbody>
</table>

*Data are given as number of patients except where indicated otherwise.
†By Fisher exact test.
‡By t test.
§Postoperative staging.

Squeeze pressures (SPs) were significantly reduced compared with baseline values before radiotherapy, indicating that internal and external anal sphincter function was altered. Another study13 focused on the morphologic features of anorectal alterations in 10 patients who developed chronic radiation proctitis after treatment for prostate carcinoma. Histologically, the main feature of radiation proctitis is marked damage to the relatively radio-sensitive myenteric plexus and hypertrophy of smooth muscle. It has been hypothesized that the internal anal sphincter, because of its fixed anatomic position and small volume, is particularly susceptible to the effects of irradiation.

In another study involving 20 patients with rectal cancer, Kusunoki et al14 demonstrated that the functional effects of irradiation on anorectal function are dose dependent. Twenty-four patients with low rectal tumors were distributed in 3 groups based on the mode of adjuvant radiation therapy. Patients who received high-dose radiation (80 Gy) had lower RPs and SPs than those treated with low-dose (30 Gy) or no radiation. The data also suggested that damage to the internal anal sphincter was predominant. However, the treatment modalities used in this particular study (high-dose intraluminal brachytherapy administered 2 weeks before surgery) differ markedly from the current protocols used in Western countries.

In another study involving 20 patients with rectal cancer, Birnbaum et al15 did not observe any alterations in anorectal function after pelvic irradiation. However, the mean distance of the tumors from the anal verge was 7.4 cm, and the treated volume was above the anal canal in 10 patients. Two years later, 3 patients from the ini-
tial group died and 4 others had undergone abdominoperineal resection.16 The authors recommended differentiating the potential injury caused by the surgical procedure itself from that caused by irradiation.

This study was undertaken to identify the manometric effects of pelvic irradiation on anal sphincter function after a PCAA for low rectal and middle rectal (<10 cm from the anal verge) tumors.

RESULTS

Forty-two successive patients were available for analysis and were included in this study. There was a male-female ratio of 3:2, and the mean patient age was 67 years (range, 42-84 years). There were 23 patients in the surgery group and 19 in the chemoradiotherapy group. Fourteen patients underwent preoperative radiotherapy and 5 underwent postoperative radiotherapy. In the latter group, ileostomy closure was performed 2 months after completion of radiotherapy. The reported adverse effects due to pelvic irradiation included dermatitis and diarrhea; in most patients, these symptoms were controlled by topical corticosteroid administration and did not result in significant morbidity. All patients completed the 6-week scheduled radiation treatment. The fluorouracil infusion was discontinued in 4 patients because of hematologic adverse effects, poor tolerance, or both.

The preoperative clinical and manometric characteristics of both groups are summarized in the Table. Patients in the chemoradiotherapy group exhibited a trend toward more advanced stage, more distal tumors, and higher RPs and SPs. However, none of these differences reached statistical significance. A colonic J-pouch was performed in 36 patients and low anterior resection was performed in 6 patients; however, a standardized dissection and stapled technique for anastomosis was used irrespective of the reconstruction technique. Eleven patients with stage II and 6 with stage III tumors did not receive adjuvant therapy, mostly because of advanced age or concern about possible adverse effects.

Postoperative RP was significantly lower in the chemoradiotherapy group compared with the surgery group (32.7 ± 17 vs 45.3 ± 18 mm Hg; P = .03 by t test). When considering the postresection-preresection RP ratio, again the reduction in RP was significantly increased by the adjunction of irradiation (0.76 vs 0.49; P = .005 by t test). In contrast, there was no significant difference between SPs in each group compared with preoperative values (postresection-preresection SP ratio, 1.10 vs 1.07 in the surgery and chemoradiotherapy groups, respectively). Squeeze pressures were also similar after surgery in the surgery and chemoradiotherapy groups (108 ± 56 vs 102 ± 52 mm Hg; P = .69).

Figure 1 and Figure 2 illustrate the RP changes in the chemoradiotherapy and surgery groups, respectively, from before to after treatment. It seems that most values in the surgery group are relatively homogeneous, whereas the distribution of data in the chemoradiotherapy group reflects wide variations. This information was clinically relevant because 2 patients in this group had a dramatic reduction in RP, which caused the surgeon to delay ileostomy closure. An anal ultrasound re-
revealed a normal configuration of internal and external sphincters. After 2 months of biofeedback therapy, however, RPs returned to levels compatible with continence, and ileostomy closure was undertaken.

The threshold for first sensation after surgery was not significantly different between the surgery (19.8±8.3 mL) and chemoradiotherapy (18.6±13 mL) groups (P=.72 by t test). Similarly, there was no difference in the maximal tolerable volume between patients who underwent a colonic J-pouch in the surgery and chemoradiotherapy groups (94±54 mL vs 102±68 mL; P=.65 by t test). Finally, the rectoanal inhibitory reflex was present after surgery in 62% and 79% of patients in the surgery and chemoradiotherapy groups, respectively (P=.89 by χ² test).

**COMMENT**

The data indicate that the current regimen of pelvic irradiation has a significant impact on internal anal sphincter function 8 to 12 weeks after PCAA in patients with rectal cancer. Mean RPs (which reflect internal sphincter function) were reduced by 51% in the chemoradiotherapy group compared with 24% in the group treated with surgery alone. Squeeze pressures (which reflect external sphincter function) were unchanged and did not differ between groups. Although RP changes seemed to be relatively homogeneous in the surgery group, the addition of radiotherapy was associated with striking intragroup variations, suggesting that susceptibility to irradiation-induced damage to the anal sphincter might be affected by individual characteristics.

Clinically, the functional results of PCAA are not optimal, even in the absence of adjuvant radiotherapy. In a study of 81 patients with coloanal anastomosis for rectal cancer, Paty et al reported that 28% of patients experienced some degree of leakage and 32% wore a pad at least part-time after median follow-up of 4.3 years. Internal sphincter dysfunction, with resulting low RPs, is a well-known component of the low anterior syndrome described after PCAA. Church et al demonstrated in a study including 16 patients with coloanal anastomosis for rectal cancer that RP values after low anterior resection were 30% lower than preoperative values. In patients treated with chemoradiation only for anal carcinomas, different authors have observed a significant reduction in RP after pelvic irradiation. Altogether, these data indicate that in patients with rectal cancer, the internal sphincter dysfunction due to surgery is further aggravated by radiotherapy at a dose of 50.4 Gy. Moreover, simultaneous delivery of large doses of fluorouracil is likely to be associated with increased normal tissue toxicity.

Three factors are likely to affect irradiation-induced damage to pelvic normal tissues: the total dose and the volume of irradiation and individual susceptibility, which is likely to be determined by the genetic characteristics of the patient. Patient-to-patient heterogeneity has been shown to affect the development of lung fibrosis after radiotherapy for lung carcinoma. Recently, it was suggested that the susceptibility to irradiation-induced damage in normal tissues was a heritable trait controlled by 2 genetic loci, one of them being localized on chromosome 17. Experimentally, Skwarchuk and Travis elegantly demonstrated that there is a critical threshold amount of rectal tissue that can tolerate a radiation dose without complication and that the threshold might vary among individuals.

Currently, there are no means to identify individuals at risk for developing irradiation-related complications. Thus, the volume of irradiation remains the only determinant of irradiation-induced toxic effects, which can be modified to minimize anorectal dysfunction without compromising oncologic outcome. Currently, most oncologists consider the lower border of the ischial tuberosity as an adequate limit for irradiation in patients with rectal cancer whenever a sphincter-preserving procedure is considered. Data from 2 large trials of preoperative irradiation (the Stockholm I and II trials) indicate that by reducing the treatment volume cranially and by using a 4-portal technique, it is possible to achieve a reduction in the rate of irradiation-induced complications.

![Figure 1](https://archsurg.jamanetwork.com/figure1.png)  
*Figure 1. Resting pressure changes in the chemoradiotherapy group.*

![Figure 2](https://archsurg.jamanetwork.com/figure2.png)  
*Figure 2. Resting pressure changes in the surgery group.*
The clinical implication of these results is that for upper and middle rectal carcinomas, the anal canal should be excluded from the field of irradiation; for low rectal cancers, if technically possible, adequate shielding of the anal sphincter should be performed. These modifications in the irradiation technique are unlikely to compromise the oncologic outcome and might have a significant impact on the quality of life of patients with pelvic malignant neoplasms. In conclusion, dysfunction of the internal sphincter, which is a significant component of the anterior resection syndrome, seems further aggravated by the current regimen of chemoradiotherapy for rectal cancer. Because a functional internal sphincter has major implications for continence and quality of life, it may be justified to introduce the concept of sphincter-preserving radiotherapy in patients with pelvic malignant disease. This concept needs to be balanced against any potential deleterious effects on oncologic outcome, which remains the primary end point. Future studies should be conducted to determine in which measure these manometric alterations correlate with clinical incontinence on a long-term basis. Finally, the molecular mechanisms responsible for irradiation-induced damage to normal tissues (which might include transforming growth factor β1 and connective tissue growth factor) should be further investigated.

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REFERENCES