

# Adjuvant Postoperative Radiation Therapy for Dukes C Adenocarcinoma of the Rectum

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This study was designed to explore the effects of adjuvant postoperative radiation therapy on the course and survival of patients with Dukes C adenocarcinoma of the rectum. Moderate dose radiotherapy was offered to 64 patients. Twenty-four accepted and were treated, while the remainder refused. With a mean follow-up of 32.3 months, the overall survival rate was 63% (40/64) and the mean disease-free survival rate at the time of this report was 45%. The following variables were analyzed separately: operative procedure, distance of the tumor from the anal verge, tumor size, and transmural, vascular, lymphatic and perineural invasion of tumor. The most significant differences between irradiated and non-irradiated patients were found in the group of patients whose lesions were 6 cm or less from the anal verge. Of the 19 such patients with an average follow-up of 36.4 months, ten patients were irradiated and nine were not irradiated. The irradiated group had a 90% (9/10) survival rate and 70% (7/10) of them were disease free; the non-irradiated group had a 44% (4/9) survival rate and 22% (2/9) of them disease free. It is concluded that patients with adenocarcinoma of the rectum metastatic to lymph nodes, whose lesions' lower border is measured 6 cm or less from the anal verge, benefit significantly from adjuvant postoperative radiotherapy.

**I**N AN EFFORT to improve the long-term salvage of patients with Dukes C adenocarcinoma of the rectum, the authors have explored the effects of moderate dose adjuvant postoperative radiation therapy. Sixty-four consecutive patients with Dukes' C carcinomas treated by anterior resection, abdominosacral resection, or abdominoperineal resection made up the study group. One operative death and three early post-discharge deaths due to intercurrent disease were excluded from the study. All patients were operated on in a single institution by one surgeon. At the first post-discharge visit, the experimental nature of the study was explained in detail to all 64 patients by the operating surgeon; 24

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patients accepted radiation and constitute the treated group and 40 refused radiation and constitute the control group.

Radiation was delivered either by a telecobalt unit or a 4-MeV linear accelerator. The general protocol called for 4500 to 5000 rads at 180 rads per fraction and 900 rads per week. One patient receiving 6000 rads was treated in another city. The whole pelvis was irradiated in all patients, some by antero-posterior opposed portals, but the majority by a four-field technique using antero-posterior and right and left lateral portals. Perineal portals were used in some patients with abdominoperineal resection. No boosts were applied. The interval between surgery and the onset of radiotherapy averaged 43.7 days, with a range of 11 to 120 days.

All pathologic materials were reassessed (by Q.V.) separately, without knowledge of treatment modality or outcome. Attention was directed toward specific histologic characteristics. Included among these were transmural invasion of tumor, degree of glandular differentiation (histologic grade), lymphatic invasion, and extramural vascular and perineural invasion of tumor. Distance of the lower border of the tumor from the anal verge was measured by sigmoidoscopy in the knee-chest position by the senior author.

Follow-up was conducted by the same individual (S.A.L.). Supplemental follow-up information was obtained from the patients' private physician in about one-third of the patients. No patients were lost to follow-up. Evidence of either distant or local disease was deemed a recurrence. Patients were classified as "free of disease" if they were either without symptoms of recurrence or without evidence of disease by diagnostic studies. No autopsies were obtained.

The statistical methods described by Peto et al.<sup>31</sup> were utilized with our data. Both survival and disease-free intervals were reviewed. Lifetables were constructed and

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the "logrank test" of significance was used. Subgroups of the original cohort were constructed on the basis of the previously mentioned histologic characteristics as well as by tumor distance from the anal verge and by operative procedure performed.

### Group Comparison

Those patients who underwent a course of adjuvant radiotherapy were designated as group R and those who did not were designated as group N. The two groups are compared in Table 1. The average age of the entire population was 66.9 years, with a range of 44 to 89 years. Group R ranged from 47 to 77 years, with a mean age of 63.6 years, and Group N ranged from 44 to 89 years, with an average of 68.9 years. No statistical difference with regard to age or sex was noted in the overall population. Group R had 15 men and nine women, while Group N had 16 men and 24 women. All patients underwent either abdominoperineal resection, abdominosacral resection, or anterior resection.

Using guidelines previously delineated,<sup>20</sup> any patient whose tumor was measured to be less than 7.5 cm from the anal verge in a man or 5.5 cm from the anal verge in a woman was a candidate for abdominoperineal resection. Candidates for abdominosacral resection had tumors that measured from the anal verge between 5.5 to 10 cm in women and 7.5 to 11 cm in men. All other patients underwent anterior resection.

In group R, nine abdominoperineal resections, 13 abdominosacral resections, and only two anterior resections were performed. Patients in group N also had nine abdominoperineal resections with ten abdominosacral resections and 21 anterior resections. Only the anterior resection patients had a statistically different representation with regard to adjuvant therapy. Analysis of this data has no significance and bearing on our final conclusions. For the entire group of 64 patients, the average distance from the anal verge was 9.1 cm. Forty-four patients, 19 in group R and 25 in group N, had lesions that measured 10 cm or less from the anal verge. Of these 19 group R patients, ten patients had abdomi-

nosacral resection and nine had abdominoperineal resection. The 25 group N patients had ten abdominosacral resections, eight abdominoperineal resections, and six anterior resections. Of the 20 more proximal lesions, there were five from group R and 15 from group N. Of patients whose tumors were 6 cm or less from the anal verge, there were ten from group R and nine from group N. The ten group R patients underwent seven abdominoperineal resections and three abdominosacral resections, while group N had seven abdominoperineal resections and two abdominosacral resections. No statistical significance was noted in these differences.

Fifty-seven patients (89%) had microscopic transmural invasion of tumor. Nine patients (37%) from group R and 11 patients (27%) from group N had tumors that were greater than 5 cm in diameter. Poor histologic differentiation was described in the tumors of eight patients (33%) from group R and 19 patients (47%) from group N. Sixteen group R patients (67%) and 21 group N patients (53%) had tumors that were described as moderate to well differentiated. No statistical difference was noted in any of these categories.

Adenocarcinoma was found in the lymphatics in eight group R patients (33%) and ten group N patients (25%), while only a total of seven patients (11%) had histologic evidence of perineural involvement. Tumor invaded the extramural blood vessels in three patients (13%) from group R and five patients (13%) from group N.

### Results

At the time of this report, there was a 63% (40/64) survival rate in the total population, with an average follow-up length of 32.3 months. Sixty-seven per cent of group R patients survived over an average of 35 months follow-up and 60% of group N survived an average of 31 months follow-up. Life tables for the entire group (Fig. 1) and comparing group R and group N (Fig. 2) are plotted.

Forty-five per cent (29/64) of the total population remained disease-free during the course of this study. In group R, 46% of the patients were without disease. The

TABLE 1. Clinical and Pathologic Features as Described in the Study Group (64 Lymph Node Positive Dukes' C Adenocarcinomas)

	Total	Age Mean	Sex M/F	Distance—ANAL Verge		Operation*			Trans- mural	Size		Differen- tiation†		Invasion		
				<10 cm	>10 cm	APR	ASR	AR		<5 cm	>5 cm	Poor	Other	Blood Vessel	Lymph Vessel	Peri- neural
Overall	64	66.9	1/33	44	20	18	23	23	44	44	20	27	37	8	18	7
Group N	40	68.9	16/24	25	15	9	10	21	29	29	11	19	21	5	10	3
Group R	24	63.6	15/9	19	5	9	13	2	15	15	9	8	16	3	8	4

\* APR = abdominoperineal resection; ASR = abdominosacral resection; AR = anterior resection.

† Differentiation: other = moderate or well.

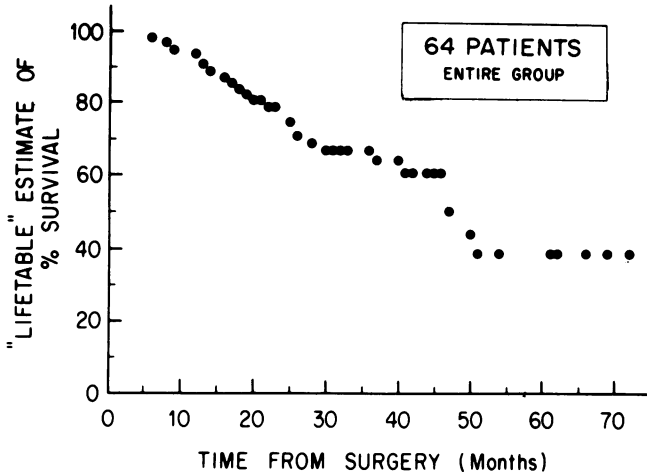


FIG. 1. Lifetable of survival for the entire patient population of Dukes C rectal adenocarcinoma.

“logrank test” for statistical significance was used here and in all subsequent calculations. No statistical significance was noted in this survival or disease-free data.

**Distance from Anal Verge**

In the population of patients whose tumors were measured to be 10 cm or less from the anal verge, there was a 61% (27/44) overall survival rate. Group R had a 79% (15/19) survival rate, while group N had 48% (12/25) rate. The life table, plotted in Figure 3, shows a statistically significant benefit to group R ( $p < 0.05$ ). In the same population, 45% of the patients (20/44) remained disease-free. Fifty-eight per cent of the patients (11/19) in group R and 36% of patients (9/25) in Group N were disease-free. Life tables for this relationship (Fig. 4) also showed a significant difference ( $p < 0.05$ ). If the

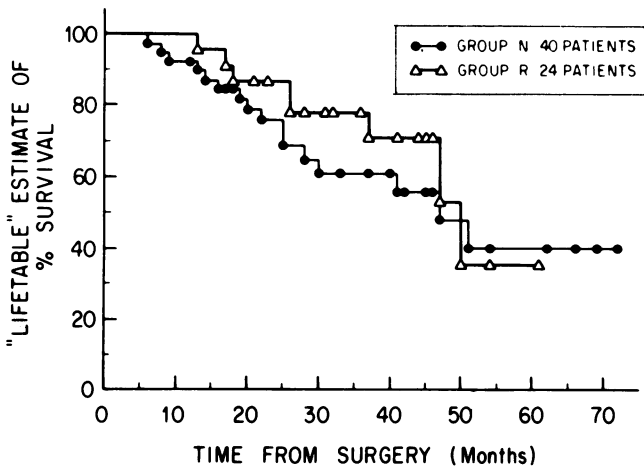


FIG. 2. Lifetable comparing survival in group R (radiated) and group N (non-radiated) in the entire patient population of Dukes C rectal adenocarcinoma.

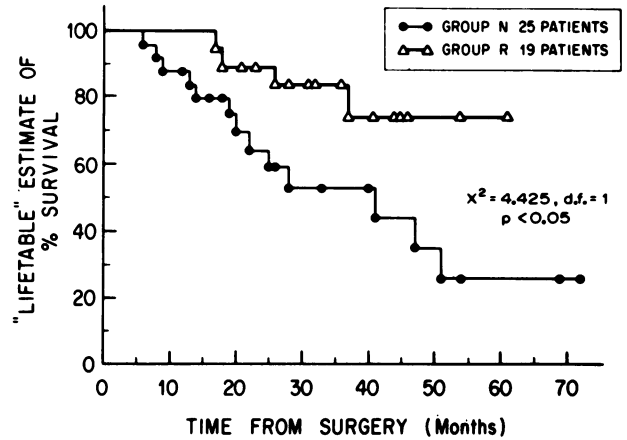


FIG. 3. Lifetable comparing survival in group R (radiated) and group N (non-radiated) in the subgroup of patients with tumors 10 cm or less from the anal verge.

data is subjected to further scrutiny, however, more significant benefit appears to be enjoyed by group R in those tumors that measured 6 cm or less from the anal verge. Conceivably, the markedly improved results in this subgroup could skew the data enough to give a spurious significant response in the group with tumors measuring 10 cm or less from the anal verge.

Of the 19 patients whose tumors were located 6 cm or less from the anal verge, the overall survival rate was 68% (13/19). There was a 90% (9/10) survival rate in the radiated group R and a 44% (4/9) survival rate in the non-radiated group. (Fig. 5) These data have a high degree ( $p < 0.03$ ) of statistical significance that is reinforced by the fact that 70% (7/10) of the radiated patients were disease-free and only 22% (2/9) of the non-radiated patients were disease-free. (Fig. 6) ( $p < 0.02$ ).

The subgroup of patients whose tumors were located

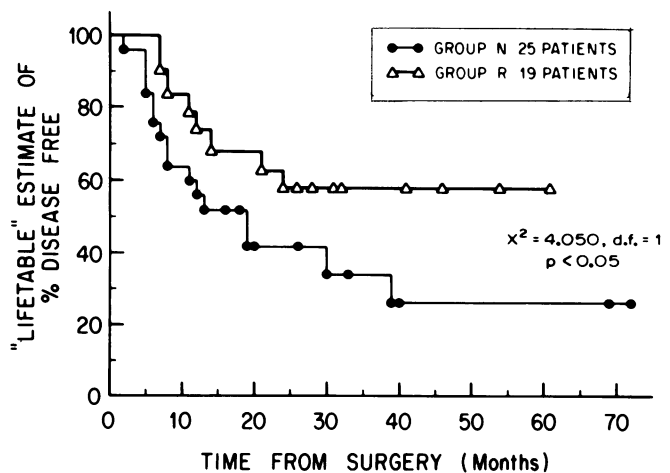


FIG. 4. Lifetable comparing per cent disease-free in group R (radiated) and group N (non-radiated) in the subgroup of patients with tumors 10 cm or less from the anal verge.

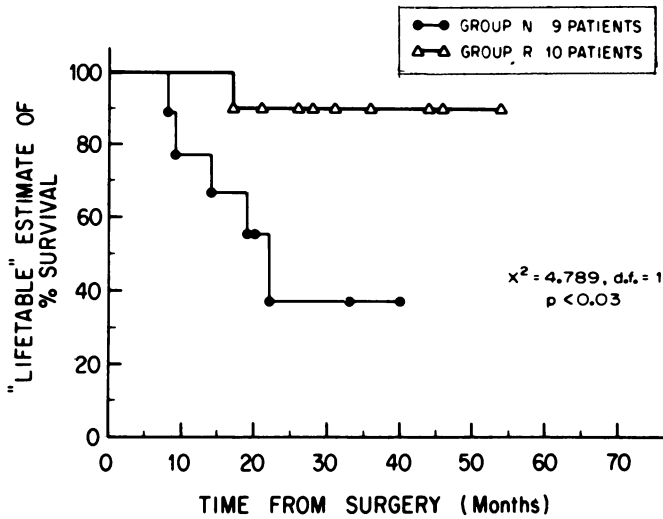


FIG. 5. Lifetable comparing survival in group R (radiated) and group N (non-radiated) in the subgroup of patients with tumors 6 cm or less from the anal verge.

between 6 and 10 cm from the anal verge were analyzed. The overall survival rate was 56% (14/25). The group R survival rate of 67% (6/9) and the group N survival rate of 50% (8/16) did not achieve statistical significance. For this same group of lesions (6–10 cm), there were 44% (11/25) group R and 44% (7/16) group N patients who were disease free. These data have no statistical significance.

**Operative Procedure**

When the population is subdivided on the basis of the operative procedure performed, there is an overall survival rate of 72% (13/18) when the procedure was abdominoperineal resection, 56% (13/23) for abdomino-

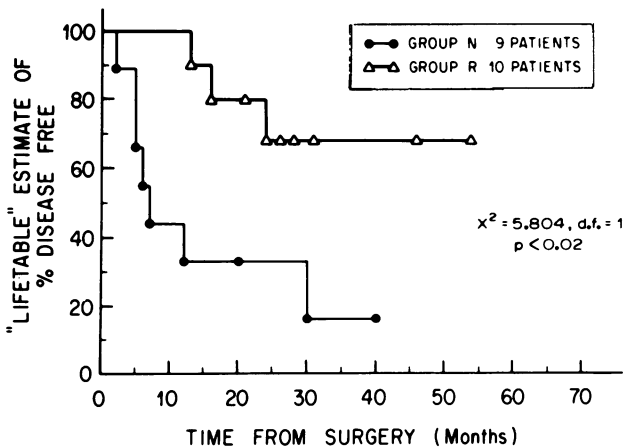


FIG. 6. Lifetable comparing per cent disease-free in group R (radiated) and group N (non-radiated) in the subgroup of patients with tumors 6 cm or less from the anal verge.

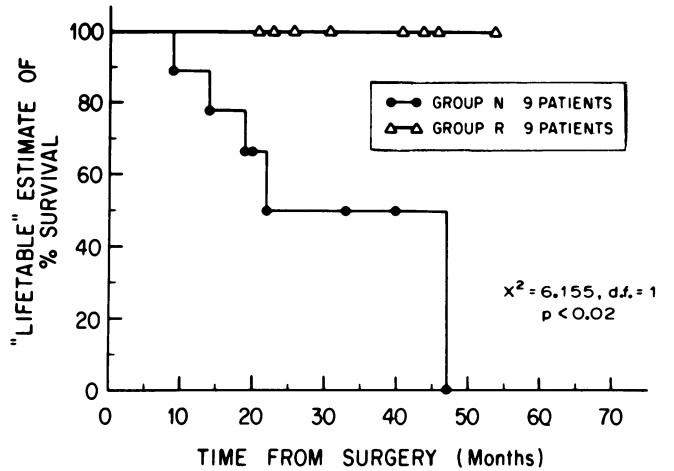


FIG. 7. Lifetable comparing survival in group R (radiated) and group N (non-radiated) in the subgroup of patients undergoing abdominoperineal resection.

sacral resection, and 61% (14/23) for anterior resection. Among patients undergoing the abdominoperineal resection, group R enjoyed a 100% (9/9) survival rate, compared to 44% (4/9) in group N. (Fig. 7) ( $p < 0.02$ ). Similarly, 78% (7/9) of group R remained disease-free, compared to 22% (2/9) of group N in those patients undergoing abdominoperineal resection. (Fig. 8) ( $p < 0.025$ ).

It must be emphasized that the abdominoperineal group contained almost all of the patients with the lesions below 6 cm. These lesions have been shown to be influenced the most by radiation.<sup>14,19,28,38,43</sup> It may be that the anatomic distance, and not the operative procedure, has influenced the results of radiation.

When the patients who underwent abdominosacral resections were analyzed, the 54% (7/13) survival rate

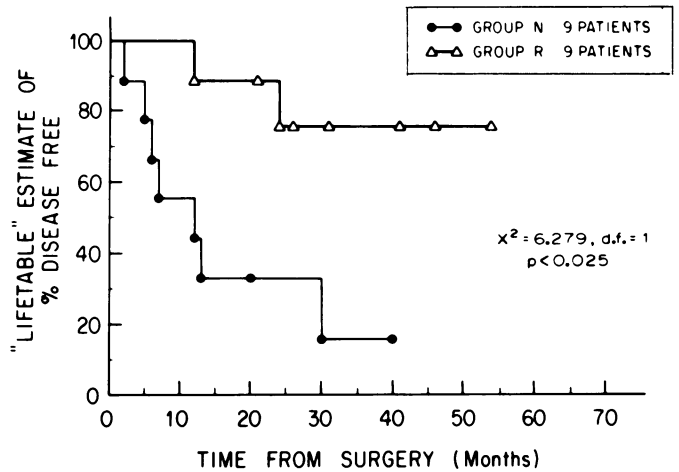


FIG. 8. Lifetable comparing per cent disease-free in group R (radiated) and group N (non-radiated) in the subgroup of patients undergoing abdominoperineal resection.

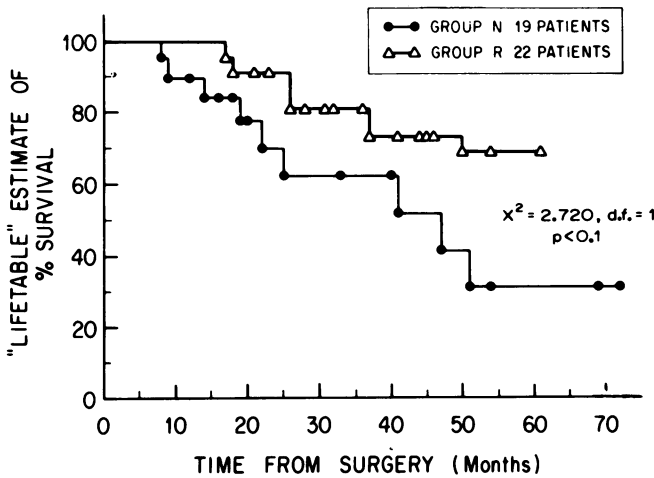


FIG. 9. Lifetable comparing survival in group R (radiated) and group N (non-radiated) in the subgroup of patients undergoing abdominoperineal resection or abdominosacral resection.

for group R was not significantly different from the 60% (6/10) survival rate for group N. The same was true for the percentage disease-free patients, with 31% (4/12) in group R and 50% (5/10) in group N. Only two of the 23 patients undergoing anterior resection were irradiated, and, therefore, comparisons were considered to have little meaning.

If a further subdivision of the population is constructed to include both the patients who were treated by abdominoperineal resection and those who underwent abdominosacral resection, there is a trend which seems to favor group R. Statistical significance, however, is not achieved. There is a 73% (16/22) survival rate in group R, compared to 52% (10/19) in group N (Fig. 9) ( $p < 0.1$ ). Fifty per cent of group R is disease-free at the time of this report, versus 37% (7/19) in group N. Again, this trend is influenced greatly by the profound difference noted in patients with lesions of less than 6 cm from the anal verge who underwent abdominoperineal resection.

### Pathological Characteristics

Transmural invasion of tumor was present in 57 of the 64 patients (89%) in this study group. Although a rare finding, patients with lymph node metastases without transmural invasion (Astler-Coller  $C_1$ )<sup>2</sup> enjoyed a 100% survival rate and suffered only one recurrence. There are four such patients in group R, but the numbers are too small for meaningful analysis. When the patients were compared on the basis of the size of the primary tumor, no significant differences were detected. The histologic characteristic of extra-mural vascular invasion by tumor was found in a total of eight patients, of whom three were from group R (13%) and five from group N (13%). The overall survival rate of 63% (5/8) differs little

from the survival rate in the whole population. Group R and group N showed no differences in this small number of patients.

A total of 18 patients had histologic evidence of lymphatic vessel invasion. The survival rate of 67% (12/18) overall revealed a 63% (5/8) survival rate for group R and 70% (7/10) for group N. Only seven patients who were examined had perineural invasion by tumor, four patients in group R and three in group N. The only pathologic finding that occurred with any degree of frequency was poor histologic differentiation that was described in 27 patients. The survival rate of patients in group R with this histologic finding was 75% (6/8), compared with 53% (10/19) in group N patients; this does not have statistical significance.

### Complications of Radiation

Diarrhea and mild urinary symptoms were quite common during the radiation course, without significant sequelae. Mild skin erythema was noted also in a majority of patients. There was one episode of late radiation enteritis with obstruction, requiring laparotomy and small bowel resection. This patient was treated in another city and received 6000 rads.

### Discussion

Although the first report of the use of radiation in the treatment of adenocarcinoma of the rectum appears in a case report by Symmonds<sup>40</sup> in 1914, very little progress was made until relatively recently. Attention was directed toward palliation or transformation to operability of unresectable lesions. Wang<sup>43</sup> reported 111 cases in 1962, treated primarily for relief of symptoms. Eighty-three per cent of the patients responded favorably to 2000 to 3000 rads, and six patients survived 5 years or more. Such data have prompted interest in radiotherapy as a primary curative measure.<sup>30,35</sup>

The first major contribution to radiotherapy as adjunct to curative resection was a series of retrospective reports from Memorial Hospital in New York.<sup>19,32,38</sup> These studies examined 1786 patients who were treated preoperatively with about 2500 rads to the pelvis. The only patients who seemed to benefit from the adjuvant treatment were those whose tumors were metastatic to local lymph nodes (Dukes C). Subsequent controlled studies at the same institution failed to confirm these findings.<sup>37</sup> A Veterans Administration Hospital cooperative study also utilized preoperative radiation and was among the first to describe the significantly smaller percentage of Dukes C tumors in their population after irradiation. The suggestion was that radiation had altered the pathologic specimen to such a degree that the routine staging must be reinterpreted. Patients who underwent abdominoperineal resection after a course of

about 2000 rads enjoyed improved 5-year survival in an uncontrolled study.<sup>14</sup> Further studies have accumulated,<sup>14,15,39</sup> but the possibility of altered pathologic data is a recognized flaw.

Many recent reports have concentrated on postoperative radiation in the dose range of 4500 to 5000 rads. Preliminary comments from M. D. Anderson Hospital<sup>33,44</sup> and Massachusetts General Hospital<sup>22</sup> suggest decreased incidence of local recurrence, but make no claims with regard to survival. Controlled, multi-institutional cooperative trials are in progress, some with a separate arm, in which combined chemotherapy and radiotherapy is offered to the patient.<sup>23</sup> A method known as the "sandwich technique" has been examined. This technique employs 500 rads in a single dose, administered immediately prior to surgery, followed by 4500 rads over 5 weeks after operation. No long-term follow-up is available yet.<sup>24,25</sup>

Radiotherapy is, by definition, a modality aimed at the control of local recurrence of disease. The relative incidence of local recurrence has been examined in considerable detail and varies, depending on the method used to document recurrence.<sup>9-13,19,42</sup> Morson<sup>27,28</sup> designated the Dukes C lesions located in the most distal rectum to be at greatest risk for local recurrence. A more recent report by Gunderson and Sosin<sup>13</sup> has reviewed the Wangenstein "second look" data to reveal a remarkably high incidence of local recurrence with the preponderance again in Dukes C low rectal tumors. Of considerable interest to the radiotherapist is the suggestion in some reports<sup>3,5,7</sup> that distant metastases may occur less frequently in the Dukes C lower third rectal lesions. These lesions at high risk for local recurrence but lesser risk for distant spread are well suited to radiotherapy.

These findings appear to be well supported by the data collected in the present report. The only subpopulation in our cohort of Dukes C patients that appeared to benefit from adjuvant radiotherapy were the patients whose tumors were located most distally. This also affirms the findings of the preoperative radiation trials.<sup>14,16,19,37</sup> Our data indicate that adjuvant postoperative radiotherapy may benefit those patients whose Dukes C tumors measure 6 cm or less from the anal verge.

It had been our intention to make use of specific histologic characteristics to define further the group of patients whose survival statistics improved with adjuvant radiotherapy. Such pathologic findings as lymphatic vessel, vascular and perineural invasion by tumors, as well as the degree of differentiation have been recognized to influence survival.<sup>8,34,36,41</sup> The only one of these characteristics that occurred with sufficient frequency to make interpretation meaningful was poor histologic differentiation. This group had a trend in favor of the patients who undersent adjuvant radiotherapy. The dif-

ference, however, was not significant. Perhaps a larger group and a longer follow-up is required to demonstrate the influence of this histologic data.

It continues to be our opinion that postoperative radiation has the advantage of an unaltered pathologic specimen. This approach also spares many patients an unnecessary course of radiation, because their tumors will be staged prior to treatment.

The possible benefits of radiotherapy must be weighed against potentially harmful side effects. The acute enteritis manifested by diarrhea is common and usually self-limited. Severe, late radiation enteritis is reported to occur in 1% to 2% of patients.<sup>16</sup> The syndrome may progress to complete obstruction or fistula formation. Patients with generalized vascular disease, such as diabetes or hypertension, are known to be at a greater risk to develop the complications. Histologic examination of radiation-injured tissues suggests occlusive vascular damage as an etiology. In addition, a small but consistent percentage of patients may develop another carcinoma after radiation.<sup>6,20</sup> The radiotherapy literature has begun to compile techniques that are intended to lessen the likelihood of major complications.<sup>4</sup> The one episode of severe, late enteritis in our population appears to be dose-related.

### Summary

A total of 64 patients with adenocarcinoma of the rectum metastatic to local lymph nodes (Dukes C) formed our cohort. Each patient was offered the option of postoperative radiation to the pelvis. A dose range of 4500 to 5000 rads was used. Twenty-four patients elected to be irradiated (group R) and 40 patients refused and were simply followed (group N). Overall survival and disease-free statistics favored neither modality. When the subpopulation with tumors located 6 cm or less from the anal verge was analyzed, a significant benefit seemed to be enjoyed by group R (90% versus 44% survival rate and 70% versus 22% disease-free). A similar relationship was found in those patients undergoing abdominoperineal resection. These data for the abdominoperineal group may be due to anatomic locations (6 cm or less) rather than the operative procedure. All pathology was reviewed independently, and such histologic characteristics as differentiation, lymphatic, perineural, and vascular invasion were assessed. No significant differences in outcome could be detected in patients with these findings.

### Conclusion

Our study suggests that patients with adenocarcinoma of the rectum metastatic to lymph nodes, whose lesions' lower border is measured to be 6 cm or less from the anal verge, benefit from adjuvant postoperative radiotherapy.

## References

- Allen CV, Fletcher WS. A pilot study on preoperative irradiation of rectosigmoid carcinoma. *AJR* 1972; 114:504-508.
- Astler VB, Collier FA. The prognostic significance of direct extension of carcinoma of the colon and rectum. *Ann Surg* 1954; 139:846-852.
- Cass AW, Million RR, Pfaff WW. Patterns of recurrence following surgery alone for adenocarcinoma of the colon-rectum. *Cancer* 1976; 37:2861-2865.
- Cohen AM, Gunderson LL, Welch CE. Selective use of adjuvant radiation therapy in resectable colorectal adenocarcinoma. *Dis Colon Rectum* 1981; 24:247-251.
- Cohen AM, Wood WC, Gunderson LL, Shinnar M. Pathological studies in rectal cancer. *Cancer* 1980; 45:2965-2968.
- DeCosse JJ, Rhodes RS, Wentz WB. The natural history and management of radiation induced injury of the gastrointestinal tract. *Ann Surg* 1969; 170:369-384.
- Dionne L. The pattern of blood-borne metastasis from carcinoma of the rectum. *Cancer* 1965; 18:775-781.
- Dukes CE. Cancer of the rectum: an analysis of 1000 cases. *J Pathol* 1940; 50:527-539.
- Floyd CE, Corley RG, Cohn I. Local recurrence of carcinoma of the colon and rectum. *Am J Surg* 1965; 109:153-159.
- Gilbertsen VA. Adenocarcinoma of rectum: a fifteen year study with evaluation of the results of curative therapy. *Arch Surg* 1960; 80:135-143.
- Gilbertsen VA. Adenocarcinoma of the rectum—incidence and locations of recurrent tumor following present day operations performed for cure. *Ann Surg* 1960; 151:340-348.
- Gilchrist RK, David VC. Consideration of pathological factors influencing five year survival in radical resection of the large bowel and rectum for carcinoma. *Ann Surg* 1947; 126:421-438.
- Gunderson LL, Sosin H. Areas of failure found at re-operation (second or symptomatic look) following "curative surgery" for adenocarcinoma of the rectum: clinicopathologic correlation and implications for adjuvant therapy. *Cancer* 1974; 34:1278-1292.
- Higgins GA, Conn JH, Jordon PH, et al. Preoperative radiotherapy for colorectal cancer (VA Surgical Adjuvant Group). *Ann Surg* 1975; 181:624-631.
- Higgins GA, Donaldson RC, Humphrey EW et al. Adjuvant therapy for large bowel cancer. Update of Veterans Administration Surgical Oncology Group Trials. *Surg Clin North Am* 1981; 61:1311-1320.
- Kinsella TJ, William DB. Tolerance of the intestine to radiation therapy. *Surg Gynecol Obstet* 1980; 151:273-284.
- Kligerman MM. Radiotherapy and rectal cancer. *Cancer* 1977; 39:896-900.
- Kligerman MM, Urdaneta N, Knowlton A, et al. Preoperative irradiation of rectosigmoid carcinoma including its regional lymph nodes. *AJR* 1972; 114:498-503.
- Leaming RH, Stearns MW, Deddish MR. Preoperative irradiation in rectal carcinoma. *Radiology* 1961; 77:257-263.
- Localio SA, Eng K, Gouge TH, Ranson JHC. Abdominosacral resection for carcinoma of the midrectum: ten year experience. *Ann Surg* 1978; 188:475-480.
- Localio SA, Stone A, Friedman M. Surgical aspects of radiation enteritis. *Surg Gynecol Obstet* 1969; 129:1163-1172.
- Mendiondo O, Wang CC, Welch JP, Donaldson GA. Postoperative radiotherapy in carcinoma of the rectum and distal sigmoid colon. *Radiology* 1976; 119:673-676.
- Mittelman A, Knowlton A, Weiland L, et al. Adjuvant chemotherapy and radiotherapy following rectal surgery: an interim report from the Gastrointestinal Tumor Study Group (GITSG). *In Adjuvant Therapy of Cancer*. New York: Grune and Stratton, 1981; 547-557.
- Mohiuddin M, Dobelbower RR, Turalba C, et al. A selective sandwich technique of adjuvant radiotherapy in the treatment of rectal cancer: a preliminary experience. *Dis Colon Rectum* 1979; 22:1-4.
- Mohiuddin M, Dobelbower RR, Kramer S, Marks G. Adjuvant radiotherapy with selective sandwich technique in treatment of rectal cancer: results of a continuing study. *Dis Colon Rectum* 1981; 24:76-79.
- Moosa AR, Ree PC, Marks JE, et al. Local recurrence after abdominoperineal resection for cancer of the rectum and rectosigmoid. *Br J Surg* 1975; 62:727-730.
- Morson BC, Vaughan EG, Bussey HJR. Pelvic recurrence after excision of the rectum for carcinoma. *Br Med J* 1963; 2:13-18.
- Morson BC, Bussey HJR. Surgical pathology of rectal cancer in relation to adjuvant radiotherapy. *Br J Radiol* 1967; 40:161-165.
- Olson RM, Perencevich NP, Malcolm AM, et al. Patterns of recurrence following curative resection of adenocarcinoma of the colon and rectum. *Cancer* 1980; 45:2969-2974.
- Papillon J. Intracavitary irradiation of early rectal cancer for cure—a series of 186 cases. *Cancer* 1975; 36:696-701.
- Peto R, Pike MC, Armitage NE, et al. Design and analysis of randomized clinical trials requiring prolonged observation of each patient. II. Analysis and examples. *Br J Cancer* 1977; 35:1-39.
- Quan SH, Deddish MR, Stearns MW Jr. The effect of preoperative roentgen therapy upon the ten and five year results of the surgical treatment of cancer of the rectum. *Surg Gynecol Obstet* 1960; 111:507-508.
- Romsdahl MM, Withers HR. Radiotherapy combined with curative surgery. Its use as therapy for carcinoma of the sigmoid colon and rectum. *Arch Surg* 1978; 113:446-453.
- Seefield PH, Barga JA. The spread of carcinoma of the rectum; invasion of the lymphatics, veins and nerves. *Ann Surg* 1943; 118:76-90.
- Sischy B, Remington JH, Sobel SH. Treatment of rectal carcinomas by means of endocavitary irradiation: a progress report. *Cancer* 1980; 46:1957-1961.
- Spratt JS, Spjut NT. Prevalence and prognosis of individual clinical and pathologic variables associated with colorectal carcinoma. *Cancer* 1967; 20:1976-1985.
- Stearns M, Deddish M, Quan S, Leaming R. Preoperative roentgen therapy for cancer of the rectum and rectosigmoid. *Surg Gynecol Obstet* 1974; 38:584-586.
- Stearns M, Deddish M, Quan. Preoperative roentgen therapy for cancer of the rectum. *Surg Gynecol Obstet* 1959; 109:225-229.
- Stevens KR, Allen CV, Fletcher WS. Preoperative radiotherapy for adenocarcinoma of the rectosigmoid. *Cancer* 1976; 37:2866-2874.
- Symonds C. Cancer of the rectum; excision after the application of radium. *Proc R Soc Med Lond [Clin Sect]* 1913-1914; 7:152.
- Talbut IC, Ritchie S, Leighton MH, et al. The clinical significance of invasion of veins by rectal cancer. *Br J Surg* 1980; 67:439-442.
- Taylor FW. Cancer of the colon and rectum—a study of routes of metastases and death. *Surgery* 1962; 52:305-308.
- Wang CC, Schulz MD. The role of radiation therapy in the management of carcinoma of the sigmoid, rectosigmoid and rectum. *Radiology* 1962; 79:1-5.