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# Radical surgery and postoperative radiotherapy as combined treatment in rectal cancer. Final results of a phase III study of the European Organization for Research and Treatment of Cancer

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**Background** There is controversy whether adjuvant radiotherapy should be given before or after surgery for locally advanced, resectable rectal cancer. Preoperative radiotherapy substantially reduces local recurrence rates but may increase postoperative complications. In addition, patients found to have early cancers are treated unnecessarily. This study is a randomized trial of postoperative radiotherapy in patients who had a potentially curative resection for locally advanced rectal carcinoma.

**Methods** Following complete excision of a Dukes B or C rectal cancer, 172 patients were randomized to adjuvant radiotherapy (46 Gy 5 days per week in 30–38 days) (84 patients) or controls (88 patients).

**Results** After a median follow-up of 85 months, no benefit from postoperative radiotherapy had been observed in disease-free survival ($P = 0{\cdot}81$), overall survival ($P = 0{\cdot}52$), local recurrence-free interval ($P = 0{\cdot}46$) or in the number and sites of recurrence. Acute toxicity following radiotherapy included diarrhoea (20 per cent), cystitis (13 per cent), delayed wound healing (7 per cent), pneumonia (5 per cent) and seizures (1 per cent). Late complications included reoperation for small bowel obstruction (5 per cent), chronic diarrhoea (20 per cent), chronic cystitis (12 per cent) and persistent perineal sinus (9 per cent). In the group who had surgery alone, late morbidity was found in 11 per cent.

**Conclusion** This trial failed to demonstrate any improvement in overall survival or local control when postoperative irradiation was given following resection of locally advanced rectal carcinoma.

The disease-free survival of patients undergoing curative surgery for rectal cancer with extension into the perirectal fat or the regional lymph nodes (or both) has not improved during the past three decades in spite of refinement of surgical technique and advances in postoperative intensive care[1]. In 50–60 per cent of patients death is caused by local recurrence[2]. However, the literature shows considerable discrepancies between local failure rates following apparently curative surgery ranging from 10 per cent or less[3] to as much as 65 per cent[4–7]. This variability may be attributed to the surgeon's skill[8], patient selection[4–7], follow-up routines[9] and statistical manipulation[10].

The patterns of local recurrence following surgery alone indicate that patients with tumour extension beyond the bowel wall or nodal involvement must be considered as having occult disease, even though their operation was potentially curative ($R_0$ resection)[5]. The main reason for such failures is the inability to obtain adequate circumferential margins in the perirectal soft tissues, where microscopic tumour often establishes initial regrowth[11]. Since most of the recurrence sites located in the pelvis could have been included in a radiation field, pelvic irradiation has been suggested[5] to reduce local recurrence rates and improve survival.

Controversy has surrounded the sequence of adjuvant radiotherapy with surgery[12]. Preoperative radiotherapy was reported to substantially reduce local recurrence rates, provided that the dosage level was 40 Gy or more in 3–4 weeks[13,14] or an equivalent biological dosage[15–17].

A randomized study conducted by the European Organization for Research and Treatment of Cancer (EORTC)[14] confirmed that preoperative radiotherapy had a clear effect on local control but it failed to show a statistically significant benefit on overall survival. A common criticism of preoperative radiotherapy is that it delays surgical resection, alters the pathological specimen, unnecessarily treats patients with early disease and increases postoperative complications.

Postoperative radiotherapy could theoretically obviate at least some of these disadvantages. Data from non-randomized trials of postoperative irradiation[18–24] suggested a possible improvement in local control rates, but properly randomized trials were lacking. This prompted the EORTC Gastrointestinal Tract Cancer Cooperative Group to initiate a randomized clinical trial to evaluate the role of postoperative irradiation in patients who had had curative surgical resection for locally advanced carcinoma of the rectum.

## Patients and methods

### *Trial design*

This was a two-arm randomized phase III trial comparing surgery alone (no adjuvant radiotherapy) with adjuvant postoperative radiotherapy following curative surgery for rectal

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cancer. The main endpoints were disease-free survival, local disease-free interval and overall survival. Local failures inside and outside the irradiated area were recorded separately.

*Eligibility criteria*

Patients were eligible for the trial if they fulfilled all of the following criteria: histological confirmation of adenocarcinoma of the rectum (within 15 cm from the anal verge); curative surgery without any macroscopic and microscopic residual tumour in the pelvis or beyond, local or metastatic, during the operation; and tumour classified as $B_2$, $B_3$, $C_1$, $C_2$ or $C_3$ in the Gunderson Sosin staging system[5]. Exclusion criteria were: age over 70 years or a Karnofsky index less than 60; previous treatment for other malignant disease except basal cell carcinoma of the skin; difficulty of follow-up for geographical problems, need to delay radiotherapy more than 8 weeks after surgery for whatever reason; and any chronic disease that could interfere with survival.

*Treatment*

The operative procedures were abdominoperineal resection (APR) and anterior resection (AR). Primary vascular ligation of the inferior mesenteric vessels was recommended, while resection of mesenteric and para-aortic lymph nodes was left to the discretion of the surgeon.

Patients randomized to radiotherapy were irradiated by a four-field technique using anteroposterior and lateral portals. The target volume included the posterior part of the pelvic cavity, the posterior region of the prostate or the posterior vaginal wall and the posterior part of the urinary bladder. Distally the target volume included the upper part of the anal canal after AR and the perineum after APR. The lateral field borders were 1 cm from the bony margin of the true pelvis at its widest point. The upper limit was the top of the fifth lumbar vertebra. Radiotherapy was delivered by 10 MV or more photon beam linac. A midplane total dose of 46 Gy was delivered, 32 Gy by anteroposterior portals and 14 Gy by lateral fields. The daily dose was 2 Gy; the patients were treated 5 days per week over 30–38 days.

*Follow-up*

Both treatment groups underwent follow-up evaluation monthly during the first 3 months, every 3 months until the end of the second year, and yearly thereafter. The investigations included physical examination, full blood count, liver function tests and measurement of serum carcinoembryonic antigen (CEA). Chest radiography and liver scans were performed at least once a year. Sigmoidoscopy or colonoscopy was performed at least once every 3 years.

Recurrence was defined as any morphological proof of the appearance of tumour by palpation, radiography, scintigraphy, laparoscopy, colonoscopy or laparotomy. Perineal recurrences after APR had to be proved by biopsy or computed tomography. A raised serum CEA level was not considered *per se* as evidence of relapse. Patients with recurrence could be treated by any method considered useful. Recurrences were reported as first failures, locoregional, distant or both. Subsequent sites of failure were not registered. After recurrence the patients were followed up to determine the duration of overall survival.

Late adverse effects were defined as symptoms and signs occurring more than 6 months after surgery.

*Statistical methods*

Patients were randomized within 8 weeks after operation and after careful control of all eligibility criteria, by telephone or fax to the EORTC Data Center. Three years after the beginning of the study, some investigators felt that it was not ethical to continue randomizing patients with $B_2$ and $B_3$ tumours. Thus, randomization was subsequently restricted to patients with Dukes C cancer.

All analyses were performed according to intention-to-treat. Survival was measured from the date of randomization to the date of death from any cause or last follow-up. Disease-free survival was measured from the date of randomization to either recurrence or death, whichever occurred first. Local disease-free interval was measured from the date of randomization to the occurrence of local failure (isolated or concomitant with distant failure) or last follow-up. Survival curves were estimated using the Kaplan–Meier technique[25] and compared by a two-sided log rank test[26]. Comparisons were adjusted retrospectively for prognostic factors using the Cox proportional hazard regression model[27]. All statistical tests were two-tailed.

Assuming a median disease-free survival of 2 years in the control group, a total of 192 events (either recurrence or death, whichever occurred first) was needed to detect an increase of 50 per cent, that is from 2 to 3 years, with a power of 80 per cent and a two-sided type I error of 0·05.

## Results

*Patient cohort*

Between October 1981 and December 1986, 172 patients were entered into this trial by 13 institutions. Fourteen patients (8 per cent) were found to be ineligible (eight in surgery alone group and six in radiotherapy group), because of age over 70 years (six patients), time elapsed from surgery to randomization longer than 8 weeks (four), sigmoid cancer (one), involved distal resection margin (one); positive para-aortic lymph nodes (one), and previous treatment for this cancer (one). Major protocol violations occurred in 12 patients (7 per cent): radiotherapy was given to four patients in the surgery alone group; radiotherapy was not given to three patients in the radiotherapy group and was interrupted after 1 week in five patients.

The fourteen ineligible patients were included in all analyses to avoid any statistical bias[28]. The median duration of follow-up was 84·7 months.

*Patient characteristics*

*Table 1* describes the patient and tumour characteristics. The median age was 59 years in both groups (surgery alone, range 28–78 years; radiotherapy, range 25–75 years; $P = 0{\cdot}721$). In the surgery alone group 62 patients had an APR and 26 patients an AR. The corresponding figures were 46 and 38 in the radiotherapy group. Less than 20 per cent of the tumours were stage B. The median distance of the tumour to the anal verge was 5 (range 0–18) cm in the surgery alone group and 6 (range 0–15) cm in the radiotherapy group ($P = 0{\cdot}078$). The two groups were comparable with regard to all standard prognostic parameters, although patients in the surgery alone group had more advanced tumour stages.

*Treatment compliance and toxicity*

Not all patients started radiotherapy within 8 weeks after surgery. The median interval was 34 (range 14–98) days. Twenty five per cent of the patients had an interval longer than 60 days. Irradiation was interrupted temporarily in 15 patients (18 per cent) because of acute diarrhoea in 12 patients. The interruption was greater than 1 week in three patients only (4 per cent). One additional patient had a definitive interruption of irradiation because of diarrhoea.

Severe acute complications occurred in two patients in the radiotherapy group, in relation to pneumonia and

**Table 1** Patient and tumour characteristics

| | Surgery alone ($n = 88$) | Radiotherapy ($n = 84$) | Total | $P$* |
|---|---|---|---|---|
| Sex | | | | 0·925 |
| M | 53 (60) | 50 (60) | 103 | |
| F | 35 (40) | 34 (40) | 69 | |
| Karnofsky index | | | | 0·912 |
| 70–80 | 4 (5) | 6 (7) | 10 | |
| 90–100 | 68 (77) | 57 (68) | 125 | |
| Unknown | 16 (18) | 21 (25) | 37 | |
| Tumour stage | | | | 0·099 |
| $B_1$ | 0 (0) | 2 (2) | 2 | |
| $B_2$ | 13 (15) | 17 (20) | 30 | |
| $B_3$ | 0 (0) | 3 (4) | 3 | |
| $C_1$ | 20 (23) | 18 (21) | 38 | |
| $C_2$ | 53 (60) | 39 (46) | 92 | |
| $C_3$ | 2 (2) | 5 (6) | 7 | |
| Tumour extension | | | | 0·195 |
| (Sub)mucosa | 0 (0) | 1 (1) | 1 | |
| Into muscle | 21 (24) | 15 (18) | 36 | |
| Full thickness | 65 (74) | 61 (73) | 126 | |
| Adjacent organs | 2 (2) | 7 (8) | 9 | |
| Tumour differentiation | | | | 0·288 |
| Well differentiated | 55 (62) | 59 (70) | 114 | |
| Moderately differentiated | 23 (26) | 18 (21) | 41 | |
| Poorly differentiated | 10 (11) | 7 (8) | 17 | |
| Venous invasion | | | | 0·978 |
| No | 61 (69) | 57 (68) | 118 | |
| Yes | 18 (20) | 17 (20) | 35 | |
| Unknown | 9 (10) | 10 (12) | 19 | |

Values in parentheses are percentages

**Table 2** Acute toxicity after radiotherapy in 84 patients

| Symptoms and signs | No. of patients ($n = 84$) |
|---|---|
| Nausea | 7 (8)* |
| Diarrhoea | 17 (20)† |
| Cystitis | 11 (13)† |
| Delayed wound healing | 6 (7)‡ |
| Dyspepsia | 1 (1) |
| Seizures | 1 (1) |
| Pneumonia | 4 (5) |

Values in parentheses are percentages. Data are missing for *ten, †11 and ‡12 patients

seizures. One patient in the surgery alone group died from pulmonary embolism. Acute morbidity related to radiotherapy is reported in *Table 2*. *Table 3* shows the late complications in both treatment groups. In the radiotherapy group, chronic diarrhoea was observed in 20 per cent of the patients, while 5 per cent had small bowel obstruction.

### *Disease-free survival*

The disease-free survival curves up to 12 years are shown in *Fig. 1*. There was no significant difference between the two groups (relative risk (RR)) = 0·95, 95 per cent confidence interval (c.i.) 0·66–1·36, $P = 0·81$). The exclusion of ineligible patients and/or patients with major protocol violations did not affect the results. The trial ended prematurely before observing the required number of

**Table 3** Long-term adverse effects after radiotherapy and surgery alone

| | Surgery alone ($n = 88$) | Radiotherapy ($n = 84$) |
|---|---|---|
| Chronic diarrhoea | 0 (0) | 17 (20) |
| Recurrent abdominal pain | 0 (0) | 6 (7) |
| Small bowel obstruction* | 1 (1)** | 4 (5)‡ |
| Persistence of perineal sinus | 9 (10)** | 7 (8)§ |
| Necrosis of colostomy | 0 of 62 (0)¶ | 1 of 46 (2)‡ |
| Chronic cystitis | 0 (0) | 10 (12)†† |
| Pelvic sclerosis | 0 (0) | 3 (4)‡‡ |
| Proctitis† | 0 (0) | 1 (1) |

Values in parentheses are percentages. *Requiring surgery or verified radiologically; †seen at proctoscopy. Data are missing for ‡one, §two, ¶three, **four, ††17 and ‡‡18 patients

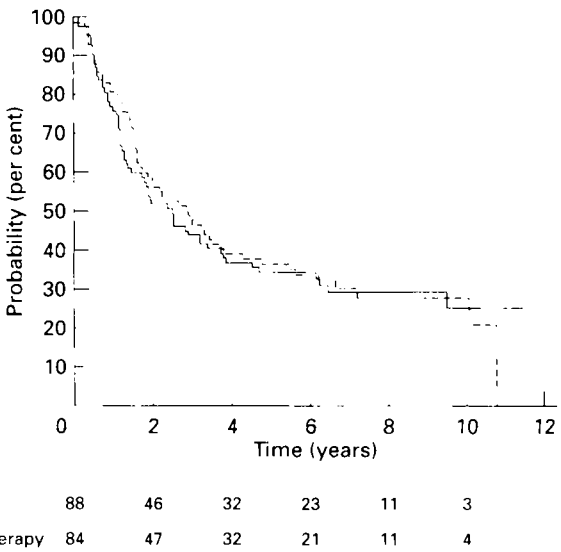


**Fig. 1** Disease-free survival in the surgery alone (———) and postoperative radiotherapy (– – –) groups. $P = 0·81$ (log rank test)

events (a total of 192). With the observed number (61 in the control arm and 59 in the radiotherapy arm), the power of the trial to detect a 50 per cent increase in the median duration of disease-free survival was 60 per cent.

### *Local disease-free interval*

Local failure occurred in 30 patients in the surgery alone group and in 25 patients in the radiotherapy group. The local disease-free interval curves are shown in *Fig. 2*. The difference between the curves was not statistically significant (RR = 0·82, 95 per cent c.i. 0·48–1·39, $P = 0·46$). Of the 25 patients in the radiotherapy group who had local recurrence, eight had a recurrence inside, one outside and six both inside and outside the radiation volume. For ten patients this information was unknown. *Table 4* reports the details of recurrent disease in the whole series.

### *Overall survival*

The overall survival data up to 12 years are shown in *Fig. 3*. The difference between the curves was not statistically

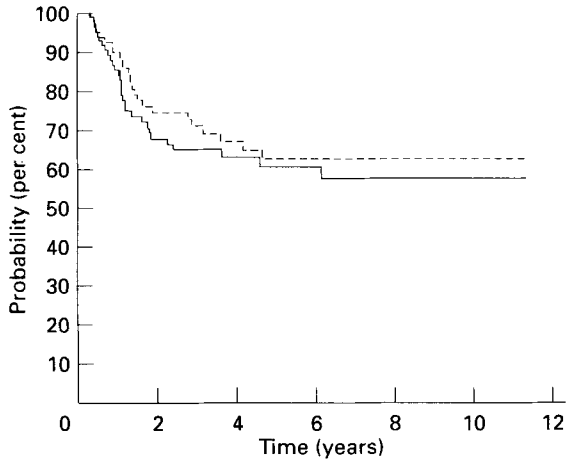


Fig. 2 Local disease-free interval in the surgery alone (———) and postoperative radiotherapy (– – –) groups. $P = 0{\cdot}46$ (log rank test)

Table 4 First sites of recurrent disease

| | Surgery alone ($n = 88$) | Radiotherapy ($n = 84$) |
|---|---|---|
| Locoregional | 26 (49) | 19 (35) |
| Distant | 23 (43) | 29 (54) |
| Locoregional and distant | 4 (8) | 6 (11) |
| Total | 53 (60) | 54 (64) |

Values in parentheses are percentages

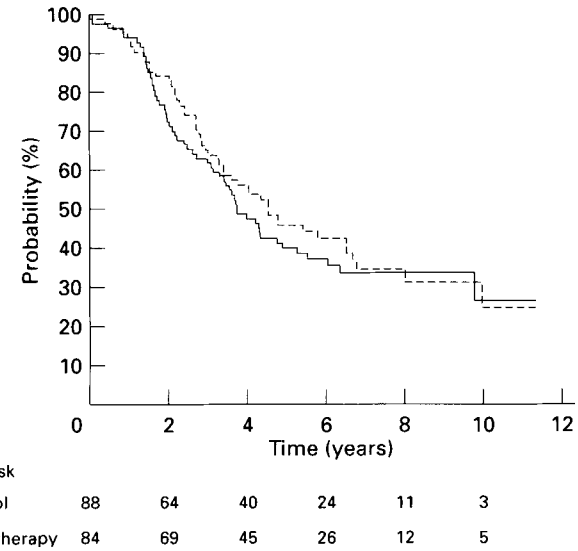


Fig. 3 Overall survival in the surgery alone (———) and radiotherapy (– – –) groups. $P = 0{\cdot}52$ (log rank test)

significant (RR = 0·88, 95 per cent c.i. 0·60–1·29, $P = 0{\cdot}52$). The exclusion of ineligible patients and those with major protocol violations did not affect the survival results. *Table 5* shows causes of death in the whole series.

Table 5 Causes of death

| | Surgery alone ($n = 88$) | Radiotherapy ($n = 84$) |
|---|---|---|
| Recurrent disease | 46 (52) | 45 (54) |
| Other primary cancer | 1 (1) | 1 (1) |
| Cardiovascular disease | 5 (6) | 5 (6) |
| Cerebral embolism | 1 (1) | 0 (0) |
| Unknown | 3 (3) | 0 (0) |
| Total | 56 (64) | 51 (61) |

Values in parentheses are percentages

## Discussion

The main aims of adjuvant treatment for locally advanced resectable rectal cancer are to increase both disease-free and overall survival while avoiding acute and late toxicity. Radiotherapy is designed to reduce local recurrence, and possibly improve overall survival.

The theoretical advantage of postoperative adjuvant radiotherapy is better selection for high-risk patients (Dukes B and C) while excluding those patients with earlier stage lesions (A and $B_1$) or synchronous liver disease. Four previously published randomized studies have compared postoperative irradiation with surgery alone for Dukes B or C patients.

In a Danish trial[29,30], a 50-Gy dose was delivered over a 7-week period with a 2-week interval after 30 Gy. Of the 244 patients allocated to radiation therapy, 20 did not receive the full dose and 11 were stopped because of intestinal complications. Twenty-five patients were reoperated for paralytic ileus or intestinal perforation. There were three toxic deaths.

In a Dutch trial[31], a 50-Gy dose was delivered over 5 weeks. Of the 88 patients allocated to irradiation, 14 were not irradiated and ten received only a 40-Gy dose because of acute intestinal complications. Late severe ileitis was observed in two patients. There was one toxic death.

In the National Surgical Adjuvant Breast and Bowel Project (NSABP) trial[32], a 46–47-Gy dose was delivered in 5·5 weeks. Among the 158 patients allocated to irradiation, four were stopped because of metastasis or refusal.

In the Gastrointestinal Tumor Study Group trial[33,34], a 40–48-Gy dose was delivered in 4·5–5·5 weeks. Of the 50 patients allocated to radiotherapy, 25 did not receive the full dose. Severe acute intestinal toxicity was observed in 16 per cent.

None of the above trials demonstrated a significant effect of postoperative irradiation on local control or on overall survival. Moreover, 12–27 per cent of the patients were not fully compliant to the planned dose and late treatment-related deaths occurred in 1–3 per cent.

This EORTC trial also failed to demonstrate an advantage of postoperative irradiation on local control and overall survival for locally advanced resected rectal cancer. In this study a slightly higher number of Dukes C patients was allocated to the surgery alone arm. This imbalance, although non-significant, could alter the results and so a correction using an adjustment method for prognostic factors was used. In any case, there was extensive overlap of the confidence intervals indicating that the local disease-free interval curves were not different. Finally, if the imbalance observed in the Dukes C distribution had influenced the results, it would have

created an artificial difference in favour of the radiotherapy arm.

Treatment compliance seems to have been better in this study than in previous trials. This may be because 25 per cent of the patients began irradiation after a 2-month interval from surgery. Lengthening the planned time interval between surgery and postoperative irradiation may result from delayed healing, infection, fatigue or practical considerations, and might reduce the radiotherapeutic efficacy[29,35–37]. While postoperative irradiation with 40–50 Gy has not shown a significant advantage in resected Dukes B or C rectal cancer, the value of an increased dose beyond 50 Gy over a carefully selected volume remains questionable. However, with regard to the high rate of acute and late effects observed with previous trials, this approach would probably result in decreased compliance and an increase in late morbidity and would not be amenable to multicentre clinical trials.

Combined postoperative radiotherapy and chemotherapy has been reported to significantly improve overall survival in comparison either to surgery alone[33,34] or postoperative irradiation[38]. However, the beneficial effect of combined postoperative radiotherapy and chemotherapy on overall survival is based on only one trial carried out on a very small number of patients[33,34].

Preoperative irradiation has definitively been proved to be effective in local disease control and on overall survival compared with surgery alone. In the earliest randomized studies low doses ranging from 5 to 20 Gy were delivered before surgery and no effect was observed[39–42]. In the eight subsequent randomized studies, moderate doses from 25 to 34·5 Gy were used[14,15,17,43–47]. All but two[43,44] demonstrated a significant reduction in local progression in all irradiated patients and a significant reduction of local recurrence in patients undergoing curative resection. Postoperative death was significantly increased in two studies using inappropriate irradiation techniques (two pelvic fields rather than four) or extended field to the para-aortic lymph node area[15,46]. In later studies, when appropriate techniques and reduced fields were used, preoperative irradiation was no longer associated with increased postoperative death and a definitive effect on overall survival was observed[17,47]. The rate of perineal wound infection is almost always increased by preoperative irradiation in patients submitted to APR.

At present, the results of this trial suggest that the next step in the treatment of locally advanced rectal cancer will be to test preoperative radiotherapy combined with an early preoperative and/or postoperative chemotherapy.

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