Review Article

How Safe is Adjuvant Chemotherapy and Radiotherapy for Rectal Cancer?

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Over the last three decades, a series of clinical trials have led to the use of adjuvant pelvic radiotherapy and chemotherapy in high-risk (T3–4 or N1) rectal cancer. There is a need to improve patient selection in order to identify the group most at risk for recurrent disease. The toxicity of adjuvant therapy should be factored into this consideration. The optimal sequencing of adjuvant therapy before or after surgery, the use of short- or long-course radiotherapy, and the utility of concurrent chemotherapy is currently being examined in randomized controlled trials (RCTs). The aim of this report was to review the morbidity and mortality in all RCTs of adjuvant therapy for rectal cancer. [*Asian J Surg* 2004;27(2):147–61]

Introduction

Over the last three decades, a series of clinical trials have led to the use of adjuvant pelvic radiotherapy and chemotherapy in high-risk (T3–4 or N1) rectal cancer. The recently reported Dutch trial,[1] where total mesorectal excision (TME) was the standard surgery, was seminal in defining the role of adjuvant therapy in rectal cancer with optimal surgery. Preliminary data showed that, with preoperative radiotherapy alone, the 2-year local recurrence (LR) rate improved from 8.2% to 2.4% ($p < 0.001$).[1] The absolute improvement in 2-year LR of 5.8% would mean approximately 17 patients would require treatment to prevent one recurrence. In addition, it is still uncertain if there is any improvement in survival. There is a suggestion that the oncological benefit of adjuvant therapy might be greater with non-TME surgery.[2]

There is a need to improve patient selection in order to identify the group most at risk for recurrent disease. The toxicity of adjuvant therapy should be factored into this consideration. The optimal sequencing of adjuvant therapy before or after surgery, the use of short- or long-course radiotherapy, and the utility of concurrent chemotherapy is currently being examined in randomized controlled trials (RCTs). The aim of this report was to review the morbidity and mortality in all RCTs of adjuvant therapy for rectal cancer.

Method

A MEDLINE literature review was performed for English language publications on adjuvant therapy for rectal cancer, from 1966 to 2002 (37 years), with the keywords rectal cancer, adjuvant therapy and randomized, controlled trial. A total of 2,191 publications on adjuvant therapy for rectal cancer were retrieved. Review articles, personal views, abstracts, non-randomized trials, pilot studies, and studies involving advanced unresectable or metastatic rectal cancers were excluded. Modalities of adjuvant therapy evaluated included preoperative radiotherapy, preoperative combined chemotherapy and radiotherapy, postoperative radiotherapy and postoperative combined chemotherapy and radiotherapy. Other modalities of adjuvant therapy such as immunotherapy, intraoperative radiotherapy and unconventional drug therapy

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were excluded. A total of 42 RCTs on resectable rectal cancer were reviewed.

The morbidities specifically sought were gastrointestinal complications (stomatitis, diarrhoea and intestinal obstruction), surgical complications (abdominal wound infection, perineal wound infection, anastomotic leak and pelvic sepsis), radiation cystitis, haematological complications and dermatological complications. In areas where there was a lack of data from RCTs, representative results from non-randomized studies are discussed.

Postoperative adjuvant combined chemotherapy and radiotherapy

Postoperative chemoradiotherapy with 5-fluorouracil (5FU) is the only adjuvant therapy shown by RCTs to reduce LR and improve survival in high-risk rectal cancer.[3–6] Protracted venous infusion (PVI) of 5FU is more effective for survival than bolus delivery.[7] The recently reported National Surgical Adjuvant Breast and Bowel Project (NSABP) R02 study confirmed the advantage of adjuvant postoperative chemoradiotherapy despite optimal surgery.[8] Adjuvant therapy significantly reduced cumulative locoregional relapse from 13% to 8% at 5 years. No survival difference was detected. However, bolus 5FU therapy rather than PVI 5FU was used during the concurrent radiotherapy phase. The toxicities of postoperative chemoradiotherapy have been reported in 11 RCTs.[3–13]

Mortality

The reported mortality rate in eight RCTs ranged from 0.3% to 4% (Table 1).[3–5,7–11] In three other RCTs, the mortality was not stated.[6,12,13] The main causes of death were sepsis (40%), intestinal obstruction or perforation (50%) and peritonitis (10%). All three deaths in the Copenhagen trial (18%) were related to severe radiation enteritis, with subsequent intestinal obstruction, perforation and sepsis.[14] The high mortality rate in this study was probably because of both the unconventional use of concurrent methotrexate, which acts as a radiation sensitizer, and the now obsolete two-field irradiation technique. The results are not presented in Table 1 as the trial was prematurely terminated after 34 patients had been treated for frequent and serious complications.[14]

Acute adverse effects

Acute gastrointestinal and haematological toxicities may be considerable and are sometimes severe or life-threatening. Major acute gastrointestinal toxicity includes severe diarrhoea (11–41%), nausea (4–38%), vomiting (2–11%) and stomatitis (5–27%). In the Gastrointestinal Tumor Study Group (GITSG) study, severe and life-threatening acute toxicities (Eastern Cooperative Oncology Group, ECOG, grades 3–4[15]) occurred in 61% of patients after chemoradiotherapy, compared with 18% and 31% after radiotherapy or chemotherapy alone, respectively.[3] Myelosuppression and severe diarrhoea are increased with combined therapy compared to either chemotherapy or radiotherapy alone.

Haematological

Haematological toxicity has been reported in all major studies of combined therapy. Leucopenia (total white cell count, $< 2 \times 10^3$/mL) occurred in 28% of the combined group compared with 2% and 13% after radiotherapy or chemotherapy alone in the GITSG study.[3] However, most of these leucopenias were without serious clinical sequelae. Krook et al reported similar data in the first North Central Cancer Treatment Group (NCCTG) study.[4] Both studies used a now unconventional combination of 5FU and methyl-chloroethylcyclohexylnitrosourea (MeCCNU), which almost certainly increased overall toxicity.

Nausea

Nausea has been reported in up to 38% of patients who receive postoperative chemoradiotherapy. The rates vary from study to study depending on whether all grades of nausea or only severe or life-threatening reactions are reported. Nausea occurred in 38% of the chemoradiotherapy group receiving 5FU alone compared with 6% in the radiotherapy alone arm in the Krook et al study.[4] When severe nausea only was considered, 2% and 0% were affected, respectively. The addition of semustine increased the risk of nausea to 73%, of which 10% was severe. O'Connell et al reported no difference in the incidence of severe or life-threatening nausea between the chemotherapy alone arm with 5FU and the chemoradiotherapy arms with PVI or bolus 5FU (1% in each arm).[7] The likelihood of developing any nausea, particularly severe nausea, is dependent on the chemotherapeutic agent used, and is worse with combination chemotherapy.[4,7]

Diarrhoea

In the Krook et al study,[4] postoperative chemoradiotherapy produced a significantly increased rate of severe or life-threatening diarrhoea (National Cancer Institute Common Toxicity Criteria ≥ grade 3[16,17]) in patients receiving bolus 5FU (22%)

compared to patients receiving postoperative radiotherapy alone (4%). The increased rates of diarrhoea during adjuvant therapy were manifested across all toxicity levels for patients receiving postoperative chemoradiotherapy. Comparing postoperative radiotherapy alone and postoperative chemoradiotherapy, the incidences of diarrhoea were as follows: grade 0, 59% vs 21%; grade 1, 20% vs 34%; grade 2, 17% vs 23%; grade 3, 4% vs 20%; and grade 4, 0% vs 2%.[16] In addition, increased rates of any diarrhoea and of severe or life-threatening diarrhoea were observed in patients who had undergone anterior resection compared to those who had undergone abdominoperineal resection (APR). In the GITSG trial,[3] grade 3–4 diarrhoea occurred in 2% of patients receiving postoperative radiotherapy alone, in 6% of patients receiving chemotherapy alone, and in 20% of patients receiving postoperative chemoradiotherapy.

The second NCCTG study demonstrated the oncological superiority of PVI 5FU over bolus 5FU when given concurrently with radiotherapy.[7] However, the rate of severe diarrhoea was significantly higher among patients who received PVI 5FU compared to bolus 5FU.[17] The risk did not appear to persist after completion of radiotherapy, indicating that at the doses used, no recall toxicity was evident. Patients who had undergone anterior resection had a higher rate of severe diarrhoea than patients who had undergone APR (31% vs 12%), consistent with the Krook et al study.[4] Otherwise, there was no significant increase in severe toxicities with PVI 5FU. Severe leucopenia is significantly more common in patients who

Table 1. Randomized controlled trials of adjuvant postoperative chemotherapy and radiotherapy for rectal cancer

Trial	GITSG 7175[3]	NCCTG Krook et al[4]	GITSG 7180[5]	NCCTG O'Connell et al[7]	Oslo[6]	INT 0114[9]	NSABP R02[8]	NSABP R03[12]	Genoa[10]	German (CAO/ ARO/ AIO-94)[11]	University of Uslan[13]
Treatment schedule	40 Gy/ 20 for 4 W + 5FU/ MeCCNU	50.4 Gy/ 28 for 5.5 W + 5FU/ semustine	40 Gy/ 20 for 4 W + 5FU/ semustine or escalating 5FU	45 Gy/ 25 for 5 W + bolus or PVI 5FU w/wo semustine	46 Gy/ 23 for 4 W + bolus 5FU	50.4 Gy/ 28 for 5.5 W + 5FU w/wo FA or FA/ levamisole or levamisole	50.4 Gy/ 28 for 5.5 W + 5FU/FA	50.4 Gy/ 28 for 5.5 W + 5FU/FA	50 Gy/ 25 for 5 W + 5FU/ levamisole	50.4 Gy/ 28 for 5 W + 5FU	45 Gy/ 25 for 5 W + 5FU/FA
N	46	104	210	660	72	1,696	694	137	110	310	308
Follow-up (mo)	94	84	70	46	96	48	93	12	28	NS	37
Complications (%)											
Mortality	4	2	4	0.3	0	1.5	1	0	1.5	1.6	0
Stomatitis	NS	27	NS	7	NS	5–12	21	NS	41	3	7
Severe diarrhoea	19	35	NS	24	11	19–35	31	12	14	13	7
Nausea	NS	38	NS	4	16	NS	NS	NS	33	3	NS
Vomiting	6	11	NS	3	4	2–5	6	NS	NS	3	4
SBO	5	5	3	5	4	6	NS	NS	NS	NS	NS
Enteritis	4	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Rectal radiation stricture	5	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Thrombocytopenia	17	9	1	15	0	1	0	NS	3	NS	0
Leucopenia	28	33	5	30	25	37–49	3	NS	20	3	3
Dermatitis	8	28	NS	3	33	NS	3	NS	9	3	1
Second primary cancer	NS	5.8	0.4	NS	NS	NS	5.9	1.6	NS	NS	NS
Completion rate (%)	65	83	83	87	89	77–82	92.5	NS	90	NS	88

GITSG = Gastrointestinal Tumor Study Group; NCCTG = North Central Cancer Treatment Group; INT = Intergroup; NSABP = National Surgical Adjuvant Breast and Bowel Project; W = weeks; 5FU = 5-fluorouracil; MeCCNU = methyl-chloroethylcyclohexylnitrosourea; w/wo = with or without; FA = folinic acid; NS = not stated; SBO = small bowel obstruction.

receive bolus 5FU. The use of folinic acid (FA) or levamisole in combination with 5FU is also associated with increased gastrointestinal toxicity without improved efficacy.[9]

Given the severity of gastrointestinal toxicity, a range of strategies has been investigated in an attempt to prevent or reduce diarrhoea during pelvic radiotherapy. Besides dietary modifications,[18] the combination of diphenoxylate and atropine (Lomotil®), and loperamide (Imodium®) has been used. In severe diarrhoea, however, excessive use of anti-diarrhoeal medication may precipitate an ileus. Other agents such as olsalazine,[19] cholestyramine[20] and sucralfate[21] are either ineffective or the related toxicity is unacceptable. More recently, octreotide has been shown in an RCT to be more effective than the combination of diphenoxylate and atropine.[22] However, octreotide is expensive and requires subcutaneous administration. Longer-acting octreotide may prove to be a more acceptable alternative.

Tolerability

Frequent and severe toxicities related to postoperative chemoradiotherapy lead to completion rates of only 65% (GITSG study[3]) and 83% (Krook et al[4]). Patients may sometimes refuse to continue with treatment. In contrast to the GITSG trial,[3] where treatment was delivered over 18 months, it is now usual to treat patients for only 6 months. As a result, the completion rate with the modern approach would be expected to be much higher; the latest studies have consistently demonstrated this, with completion rates at around 85% to 95%.[7,8,10,13] Early radiotherapy treatment commencing with the first cycle of chemotherapy demonstrated not only improved disease-free survival but also improved patient compliance.[13] Radiotherapy of 40 Gy or more was given to 96% of patients who had early chemoradiotherapy compared with 90% who had late chemoradiotherapy.

In the Copenhagen trial, acute toxic symptoms were noted in many patients, and included nausea (100%), vomiting (100%), diarrhoea (100%), stomatitis (40%), and severe radiation cystitis (11%).[14] Possible reasons for the very high level of toxicity were the use of a two-field technique incorporating large irradiated volumes (upper level of field at L2 vertebral level) and the combined use of methotrexate, a known radiation sensitizer. These techniques are no longer used.

Late adverse effects

Long-term radiation effects include radiation enteritis (up to 4%), small bowel obstruction (SBO) (up to 5%), and radiation stricture (up to 5%).

Radiation enteritis

In the GITSG study,[3] all the five patients (4%) with radiation enteritis required laparotomy and two died. In the Krook et al study,[4] SBO requiring surgery occurred in 7% of patients receiving chemoradiotherapy. The higher incidence of SBO after postoperative radiotherapy compared with preoperative radiotherapy may be secondary to postoperative adhesions and the prolapse of small bowel loops into the irradiated pelvis. The incidence of SBO increases by 30% to 40% if the radiation fields extend higher into the abdomen.[23–25] The extent of this problem seems to be related to the volume of the irradiated small bowel. This underscores the importance of precise radiation techniques that exclude the small bowel from the irradiated fields. Methods to reduce this exposure include small bowel contrast (gastrografin) to highlight the small bowel position, treatment in a prone position with a full bladder or on a belly board to force the small bowel in a cephalad direction, multiple radiation fields to reduce the volume of the irradiated small bowel and dosimetric hot spots, and appropriate shielding.[26] However, in the postoperative setting, irradiation of adherent small bowel loops can still occur. Surgical manoeuvres and devices such as an omental sling, resorbable polyglycolic-acid mesh, reperitonealizing the pelvic floor or suturing the posterior wall of the bladder to the pelvic sidewalls may be used.[27–31] However, despite these surgical manoeuvres, prolapse of the small bowel into the pelvis and radiation of loops of small bowel at the pelvic brim can still occur.[32,33]

More recent publications have reported a lower incidence of SBO requiring surgery. This may be related to better surgical or radiotherapy techniques. The O'Connell et al study,[7] which used a bolus 5FU arm similar to the original Krook et al study,[4] reported this complication in only 3% of patients. The PVI 5FU arm was similar, with 4% of patients affected. The Intergroup 0114 trial reported this complication in 6% of patients but included those who required surgery as well as patients receiving conservative inpatient hospital care.[9]

Bowel function

While there are no long-term prospective randomized controlled data on bowel function following postoperative chemoradiotherapy, retrospective studies suggest a range of detrimental effects.[34,35] Patients receiving postoperative chemoradiotherapy had more bowel movements per day, clustering of bowel movements and nocturnal bowel actions. More of these patients wore a pad and were unable to defer defaecation for more than 15 minutes. They also had a higher incidence

of liquid than firm stools, greater use of anti-diarrhoeal medications, more perineal skin irritation, more difficulty in differentiating stool from gas, and more stool fragmentation. It is probable that the clinical consequences of postoperative chemoradiotherapy are related to decreased rectal capacity and compliance. However, changes in rectal motor and sensory function and changes in surrounding soft tissues may also contribute. Anal sphincter function might be affected if it is within the radiation fields, as is required with a low rectal cancer.

Sexual function

Sexual function after adjuvant chemoradiotherapy was not evaluated formally in any of the RCTs. There are retrospective reports of dyspareunia in women and impotence (5%) in men.[35] The effect of adjuvant chemoradiotherapy on fertility and menstrual status is not clear, although moderate to high doses (≥ 20 Gy) of radiotherapy are known to sterilize most fertile women.[36] Chemotherapy alone may cause early menopause, especially in older women receiving adjuvant treatment for breast cancer;[37] however, there are no available data on 5FU.

Second malignancy

One well-recognized late effect of radiotherapy is an increased risk of a second primary malignancy within the radiation field. A second primary cancer developed in 5.8% of patients in the Krook et al study,[4] affecting the brain, breast, colon, endometrium, kidney, larynx, lip, lung and pancreas. The NSABP R02 trial reported second primary cancers in 5.9% of patients, with an increased rate of colon and prostate cancer in the 5FU, semustine and vincristine (MOF) arm (8.7% with MOF vs 7.7% without MOF).[8] Other cancers such as lung, bladder, breast and malignant melanoma were evenly distributed across the four chemotherapy regimens. There was no reported leukaemia or blood dyscrasia. These observations have not been reported in any other major study. The GITSG study reported an increase in acute non-lymphatic leukaemia after exposure to MeCCNU, but this known leukaemogenic agent is no longer used.[3]

Postoperative adjuvant radiotherapy alone

Eleven RCTs on postoperative radiotherapy alone for stage II–III resectable rectal cancer were reviewed.[4,10,25,38–45] Most studies used modern radiotherapy techniques with at least three fields and radiation doses of 40 to 60 Gy with conventional fractionation (1.8–2.3 Gy). Postoperative radiotherapy alone is now rarely used except in the management of a locally excised small rectal cancer or if the patient refuses chemotherapy.

Mortality

Mortality after postoperative radiotherapy varies from 0% to 5% (Table 2). The Uppsala study reported the highest mortality,[38] whereas other studies reported rates of 1% to 2%.[10,25,39] A possible reason for the discrepancy is the older patient population in the Uppsala study (median, 70 years). Total radiation doses were also higher (60 Gy). Five of the 10 deaths in the Uppsala study were possibly caused by radiotherapy-related complications such as anastomotic dehiscence (n = 1), sepsis (n = 1), and ileus (n = 3). Deaths often followed surgical intervention for radiotherapy-related complications such as SBO from complex adhesions or radiation enteritis.

Acute adverse effects

Acute toxicities after postoperative radiotherapy for rectal cancers are shown in Table 2. Gastrointestinal, urological and dermatological complications were noted. Diarrhoea (8–48%), nausea (4–17%), skin reactions (8–28%), radiation cystitis (6–12%) and fatigue (14%) were common. Because of these toxicities, a proportion (12–50%) of patients did not complete the planned radiation dose. The completion rate of postoperative irradiation in the Uppsala study was only 49%,[38] whereas it was 85% in the Danish study[25] and 73% in the Rotterdam trial.[39] Possible reasons were an older patient population and a higher total radiation dose in the Uppsala trial. However, criteria for ceasing radiotherapy were not clearly defined.

Although most toxicities are mild, more serious complications requiring hospitalization or surgical intervention do occur. In the Uppsala trial, five (7%) patients required hospitalization for parenteral nutrition because of severe diarrhoea.[38] Severe (ECOG grade 3–4[15]) gastrointestinal toxicities were observed in 4% of patients in the GITSG trial.[3,40]

Late adverse effects

SBO occurs in 5% to 11% of patients after postoperative radiotherapy.[4,38,41,42] Ileus and intestinal perforation are more common if the radiation dose delivered is more than 45 Gy.[25] In the Danish study, 10% of patients required further operations for SBO or intestinal perforation.[25] All five patients with intestinal perforation had received a radiation dose of more than 45 Gy. The addition of chemotherapy did not appear to increase the incidence of SBO.

The European Organisation for Research and Treatment of Cancer (EORTC) trial of postoperative pelvic radiotherapy with or without elective irradiation of para-aortic nodes and liver reported an increased incidence of severe late intestinal

Table 2. Randomized controlled trials of adjuvant postoperative radiotherapy for rectal cancer

Trial	No. of fields	Total dose (Gy)/ no. of fractions	*N*	Mortality (%)	Morbidity	Completion rate (%)
Denmark[25]	3	50/25	244	2	Ileus 10% Perforation 10%	85
GITSG 7175[40]	2	43.5/24	50	0	Radiation enteritis 4%	NS
NSABP R01[44]	2	47/26	184	0	Not increased but details NS	84
NCCTG Krook et al[4]	3–4	50.4/28	100	1	Diarrhoea 47% Severe diarrhoea 5% SBO 4% Radiation enteritis 1%	98
ANZ-BCT[45]	4	45/25	36	NS	Diarrhoea 38% Nausea 14%	95
Rotterdam[39]	3–4	50/25	88	1	Diarrhoea 48% Nausea 17% Radiation enteritis 2.6% Leucopenia 19%	73
Uppsala[38]	3	60/30	235	5	SBO 11% Radiation cystitis 6% Skin reaction 12%	49
UKMRC[41]	2	40/20	234	NS	Diarrhoea 46% Nausea 4% Urinary symptoms 8% Skin reaction 28% Anastomotic stenosis 20% SBO 4%	78
EORTC[42]	4	46/23	84	0	Chronic diarrhoea 20% Chronic cystitis 12% Delayed wound healing 7% SBO 5% Perineal sinus 5% Pneumonia 5%	72
Genoa[10]	4	50/25	108	0	Diarrhoea 43% Severe diarrhoea 5% Nausea 2% Skin reaction 30%	90
EORTC[43]	Limited-XRT 4	50/25	229	1	Severe late intestinal complications: 26/167 at risk	87
	Extended-XRT 4 plus 2	50/25 plus 25/19	222	1	Severe late intestinal complications: 18/158 at risk	72

GITSG = Gastrointestinal Tumor Study Group; NSABP= National Surgical Adjuvant Breast and Bowel Project; NCCTG = North Central Cancer Treatment Group; ANZ-BCT = Australia and New Zealand Bowel Cancer Trial; UKMRC = United Kingdom Medical Research Council; EORTC = European Organisation for Research and Treatment of Cancer; NS = not stated; SBO = small bowel obstruction; XRT = irradiation.

complications in patients who were randomized to the extended fields.[43] Among the 167 patients at risk in the pelvic radiotherapy arm, 26 developed severe late intestinal complications, 18 of whom required surgery. Among the 158 patients at risk in the extended field arm, 18 developed severe late intestinal complications, of whom 11 required surgery. No survival difference was seen, demonstrating the futility of treating higher-echelon lymph nodes.

Of all the RCTs investigating the role of postoperative radiotherapy in rectal cancer, only the Danish study has produced follow-up data on long-term bowel function.[46] Compared to patients who did not receive postoperative radiotherapy, those who received postoperative radiotherapy had more bowel movements per day, greater faecal urgency, more faecal incontinence, and wore a pad more often. They also had stool of liquid consistency, used anti-diarrhoeal medications more often, had perineal skin irritation, and were less able to differentiate stool from gas. This agrees with the results of a detailed retrospective report of long-term bowel function in patients receiving postoperative chemoradiotherapy.[35] The mechanisms underlying the dysfunction would presumably be no different. Whether chemotherapy further worsens anorectal function is unknown.

Preoperative adjuvant radiotherapy alone

Preoperative radiotherapy is either administered as short-course radiotherapy or over a longer course with concurrent chemotherapy. Long-course radiotherapy was arrived at empirically and is based on experiments demonstrating that the minimum dose required to eradicate micrometastases ranges from 45 to 50 Gy in 1.8 to 2 Gy fractions for 5 weeks.[47,48] The short-course variation that is used widely in Europe was developed for practical and economical reasons, allowing the radiotherapy to be delivered in 1 week with surgery accomplished the following week. The chosen regimen of 25 Gy in five fractions is considered biologically equivalent to long-course radiotherapy for late effects.[49,50] The relative merits of long-course and short-course radiotherapy have been reviewed elsewhere.[51]

A total of 21 RCTs of preoperative radiotherapy for resectable rectal cancer were evaluated (Tables 3 and 4).[1,2,41,52–68] In these studies, dosing schedules included 20 to 25 Gy in five fractions and 40 to 54 Gy in 20 to 30 fractions. Notably, in this indirect comparison, there was no significant difference in complication rates between short- and long-course radiotherapy, apart from a higher incidence of perineal wound infection after abdominoperineal excision of the rectum in patients who received preoperative high-dose, short-course radiotherapy.[1,2,57,58]

Mortality

The mortality after long-course radiotherapy was 0% to 6.6%, and after short-course radiotherapy was 0% to 9% (Tables 3 and 4). Four studies contributed to the higher end of the range (7.6–9%) with short-course radiotherapy.[56–58,60] All four trials used a two-field irradiation technique encompassing at least the upper level of the second lumbar vertebra, with the consequence that a large volume was irradiated. The excess mortality was mostly demonstrated in elderly patients (> 75 years), in whom the causes of death were predominantly cardiovascular and infectious complications, with thromboembolism (13%) accounting for most deaths.[60] The causal relationship between irradiation and cardiovascular disease is not apparent, but the risk appears to be increased when large volumes are irradiated.

It is notable that in the Stockholm (I/II) trial,[58] mortality was reduced from 8% to 2% when a four-field rather than a two-field irradiation technique was used. In more recent trials, three- and four-field irradiation techniques were used to limit the superior border of radiotherapy to L5–S1. In the Uppsala trial,[61] where the same radiation dose and schedule were used with a three-field technique, no increase in postoperative mortality was found. Similarly, in the Swedish Rectal Cancer Trial (SRCT) involving 583 patients,[2] the use of a three- or four-field technique did not affect postoperative mortality. Mortality in the surgery-alone vs three- or four-field technique arms was exactly the same (2.6% in each arm). In hospitals that, for unexplained reasons, used a two-field technique, the postoperative mortality was increased. The Dutch trial,[1] which mandated a three- or four-field technique, demonstrated no increase in postoperative mortality. Surprisingly, the United Kingdom Medical Research Council (UKMRC) trials[41,55] and EORTC trial,[64] which used a two-field technique, reported no increase in postoperative mortality. This raises the possibility that increased mortality is an effect of large fraction size.

Acute adverse effects

Short-term (acute) complications of preoperative radiotherapy include lethargy, nausea, diarrhoea (7–30%) and skin erythema or desquamation (< 5%). These acute reactions develop to some degree in most patients during treatment but are self-limiting and usually resolve within weeks of completion.[2,41,55,56]

Neuropathy

The frequency of acute lumbosacral plexopathy during and after short-course preoperative radiotherapy for rectal cancer has been reported to be as high as 6%.[69] In this series, the pain was usually localized in the lower lumbar region and of short duration, but pain was persistent in approximately 1% of

Table 3. Randomized controlled trials of adjuvant short-course preoperative radiotherapy for rectal cancer

Trial	No. of fields	Total dose (Gy)/no. of fractions	*N*	Mortality (%)	Morbidity
Memorial[52]	2	20/8	376	5.3	NS
VASOG[53]	2	20/10	347	NS	NS
Toronto[54]	2	5/1	60	0	0
UKMRC 1b[55]	2	20/10	272	3.3	Wound infection 10% Perineal wound infection 23% Pelvic sepsis 8% Anastomotic leak 8%
UKMRC 1a[56]	2	5/1	277	8	Wound infection 11% Perineal wound infection 16%
Stockholm[57]	2	25/5	170	7.6	Wound infection 11% Wound dehiscence 5% Anastomotic leak 14% SBO 4%
Stockholm I[58]	2	25/5	424	8	Wound infection 14% Anastomotic leak 13%
Stockholm II[58]	4	25/5	557	2	SBO 13.3% Thromboembolism 7.5% Femoral/pelvic fractures 5.3% Postoperative fistula 4.8%
Uppsala[38]	3	25.5/5	236	3	SBO 5% Radiation cystitis 2% Skin reaction 2%
NW England[59]	3	20/4	143	NS	NS
St. Marks[60]	2	15/3	228	9	Perineal wound breakdown 26% Anastomotic leak 15% Thromboembolism 13%
SRCT[2]	3–4	25/5	583	4	Wound infection 4.5% Perineal wound infection 20% Anastomotic dehiscence 4.7% Ileus 4.8%
Uppsala[61]	3–4	25/5	632	NS	NS
Dutch[1]	3–4	25/5	924	4	Diarrhoea 2% Increased blood loss* Ileus 5% Perineal wound infection 29% Cardiac 5%

VASOG = Veterans Administration Surgical Oncology Group; UKMRC = United Kingdom Medical Research Council; SRCT = Swedish Rectal Cancer Trial; NS = not stated; SBO = small bowel obstruction. *Blood loss: 1,000 mL with radiotherapy vs 900 mL without radiotherapy (no percentage given).

patients. Acute neurogenic pain was more common in women than men and in patients with underlying diabetes mellitus or neurogenic disorders. These symptoms are thought to be the result of acute radiation damage to the peripheral nerves and theoretically can be eliminated by avoiding irradiation above the pelvis. However, in the Dutch trial,[1] where the upper level of the radiation field was situated at the L5–S1 junction, such symptoms were reported in 53 patients, 18 of whom required interruption of treatment.

Wound complications

In all trials using moderate- or high-dose preoperative radiotherapy, a higher incidence of perineal wound infections has been reported among patients following abdominoperineal excision of the rectum. A two-fold increase in this complication was seen with both short- and long-course radiotherapy. However, when the perineum is not included in the target volume, there is no increase in perineal wound complications.[11]

Anastomotic complications

There is no reported increase in the dehiscence of colorectal anastomosis (7–15%) or ileus (5%) following preoperative radiotherapy. The reported incidence of clinically symptomatic anastomotic leaks after an anterior resection is 3% to 11%. This lack of anastomotic complications may be related

Table 4. Randomized controlled trials of adjuvant long-course preoperative radiotherapy for rectal cancer

Trial	No. of fields	Total dose (Gy)/no. of fractions	*N*	Mortality (%)	Morbidity
Yale[62]	2	46/23	15	6.6	NS
VASOG[63]	2	31.5/18	180	0.6	Thromboembolism 7.7% Septic complication 12.5% Haematological complication 7.1%
EORTC[64]	2	34.5/15	166	4.6	Wound infection 15% Perineal wound infection 48% Perineal sinus 21% Cystitis 20%
Sao Paolo[65]	2	40/25	34	2.9	Radiation cystitis 8.8% Skin reaction 5.8%
Norway[66]	2	31.5/18	159	4.2	Wound infection 5.5% Perineal wound infection 8% SBO 13% Diarrhoea 30% Skin reaction 5%
Florida[67]	4	45/25	112	0	Ileus 5% Wound infection 5% Urinary retention 9% Presacral fistula 1% Re-operation 5.2%
UKMRC 2[41]	2	40/20	139	3.5	Wound infection 6% Perineal wound infection 7% Pelvic sepsis 17% Anastomotic leak 7%
Lyon R90-01[68]	3	39/13	201	3.5	Anastomotic complication 17.5% (fistula, intra-abdominal abscess, peritonitis)

VASOG = Veterans Administration Surgical Oncology Group; EORTC = European Organisation for Research and Treatment of Cancer; UKMRC = United Kingdom Medical Research Council; NS = not stated; SBO = small bowel obstruction.

to resection of the irradiated rectum and construction of the colorectal anastomosis in a healthy undamaged portion of the rectum. A diverting stoma is generally recommended because of the extensive pelvic dissection often necessary and distal colorectal anastomosis.

Late adverse effects

In the Stockholm I trial,[58] the use of high-dose short-course preoperative radiotherapy with larger irradiated volumes led to an increase in thromboembolic events (7.5%), femoral neck and pelvic fractures (5.3%), delayed perineal wound healing (20%), intestinal obstruction (13.3%), and postoperative fistula (4.8%). Pelvic fractures occurred only among patients treated in Stockholm, where radiation shielding was not part of routine practice. However, when a four-field technique with the same radiation dose was used in the Stockholm II trial,[58] there was no increase in these complications, suggesting that precise target volume definition may help to avoid unnecessary exposure of normal tissues. The Dutch trial reported no increase in femoral neck and pelvic fractures in patients receiving preoperative radiotherapy.[1] However, it reported a statistically significant increase in cardiac events (5% vs 3%), which again emphasizes the impact of fraction size on the cardiovascular system.

Small bowel obstruction

The incidence of SBO is approximately 5% to 13% in patients receiving preoperative radiotherapy.[38,58,66] The risk is related to total dose, dose per fraction, number of radiation fields and volume of small bowel included in the radiation field.[23] This complication increases as the total radiation dose increases, as shown by the Norwegian study[66] and the postoperative radiotherapy trials (40–60 Gy).[25] Larger radiation fields will also mean a greater volume of small bowel being irradiated, as reported in the Stockholm I trial,[58] where higher field placement (upper level at L2) and a two-field technique led to much larger volumes of small bowel being irradiated. This was not shown in the SRCT and Dutch trials,[1] where small bowel exposure was minimized.

Sphincter function

The impact of preoperative radiotherapy on sphincter function remains uncertain. The SRCT trial showed that short-course preoperative radiotherapy had a negative impact on anal function.[70] There was an increase in bowel frequency, urgency and faecal incontinence. However, the anus was included in the radiation fields, which could induce direct damage to the anal sphincters and the pudendal nerves. Damage to the sphincters can result in postradiation fibrosis, especially if the biologically equivalent doses calculated for high-dose short-course radiotherapy for the sphincters are inaccurate. To date, the investigators from the Dutch trial have not reported on late complications.[1] In the Lyon study,[68] long-course preoperative radiotherapy using conventional fractionation does not appear to incur the same level of anorectal dysfunction. We await more detailed functional data from the German[11] and Polish studies,[71] which are now completed.

Data on sexual dysfunction are limited. Results from the Dutch trial[72] suggest that radiotherapy had little or no adverse effect on sexual function, above and beyond that induced by surgery.

Preoperative adjuvant combined chemotherapy and radiotherapy

The use of preoperative adjuvant combined chemotherapy and long-course radiotherapy has been adopted as standard treatment in many centres outside Europe, despite a lack of RCTs.

This approach commences with long-course conventionally fractionated radiotherapy concurrently with PVI or bolus 5FU followed, after a 6- to 8-week interval, by surgical resection and further postoperative bolus 5FU chemotherapy. The radiotherapy technique is no different to that given in the postoperative setting, using computed tomography simulation where available and small bowel exclusion protocols (e.g. multiple radiation fields). The radiation dose may vary but will always consist of a minimum of 45 Gy delivered to the pelvis, which may be followed by a boost of 5.4 Gy to the gross tumour volume in 1.8 Gy fractions delivered at five fractions/week over 5.5 weeks.

The first randomized trial of preoperative combined chemotherapy and radiotherapy was conducted by the EORTC and published in 1984.[73] A number of RCTs have recently been completed or are about to complete accrual (Table 5).[11,12] The most important of these is a large German study in which patients were randomized to either pre- or postoperative combined-modality therapy.[11] This study has just been completed. Two other similar studies, the NSABP R03[12] and the INT1047, were both terminated prematurely due to poor patient accrual.

Mortality

The mortality after preoperative chemoradiotherapy in three published RCTs ranged from 1.6% to 8.9%. The causes of death

Table 5. Randomized controlled trials of adjuvant preoperative and postoperative chemotherapy and radiotherapy for rectal cancer

	NSABP R03[12]		German (CAO/ARO/AIO-94)[11]	
	Postoperative RT (50.4 Gy) + 5FU/LV	Preoperative RT (50.4 Gy) + 5FU/LV	Postoperative RT (50.4 Gy) + 5FU	Preoperative RT (50.4 Gy) + 5FU
n	57	59	310	318
Mortality (%)	2	4	1.2	1.6
Complications (%)				
Severe diarrhoea	23	39	12	9
Nausea/vomiting	10	10	3	3
Small bowel obstruction	6	3	3	1
Fistula formation	NS	NS	1	3
Anastomotic leak	4	9	12	13
Delayed wound healing	2	3	6	5
Postoperative bleeding	NS	NS	4	3

NSABP = National Surgical Adjuvant Breast and Bowel Project; RT = radiotherapy; 5FU = 5-fluorouracil; LV = leucovorin; NS = not stated.

were mainly cardiovascular and pulmonary related.

In the EORTC trial,[73] 247 patients were randomly assigned to receive preoperative radiotherapy with or without 5FU. The mortality rate was higher among patients receiving preoperative combined therapy (8.9%) than preoperative radiotherapy alone (5%).

A preliminary report from the NSABP R03 study,[12] where patients were randomly assigned to receive either pre- or postoperative chemoradiotherapy using modern techniques, recorded two deaths in the preoperative group and one in the postoperative group. The causes of death were myocardial infarction ($n = 2$) and pulmonary embolism ($n = 1$). A similar progress report from the German study detailed the deaths of three patients in the preoperative chemoradiotherapy arm while receiving therapy.[11] This included two deaths from myocardial infarction occurring during or shortly after the first 5FU chemotherapy cycle and one case of pulmonary embolism. Two patients died after surgery, from cardiac failure and sepsis, respectively. In the postoperative chemoradiotherapy arm, three patients died after surgery and one died from pulmonary embolism while receiving postoperative therapy. Thus, preliminary data from contemporary studies have not shown any increase in mortality with preoperative combined-modality therapy.

The higher mortality rate in the EORTC study was thought to be consistent with the more elderly patient population, which included a large number of patients with coexisting cardiovascular and pulmonary diseases. Another possible explanation was the antiquated two-field technique, a risk factor, especially in elderly patients with co-existent cardiovascular diseases.

Acute adverse effects

Acute and severe adverse effects were encountered in six patients treated with chemoradiotherapy in the EORTC trial.[73] Other side effects were diarrhoea (33%), nausea and vomiting (18%), and muscular weakness (14%). Acute side effects were less common with preoperative than postoperative chemoradiotherapy. In the NSABP R03 study,[74] which was recently updated after the enrolment of 267 patients, more patients tended to have grade 4–5 toxicity in the preoperative arm compared with the postoperative arm (34% vs 23%; $p = 0.07$). The largest difference was in grade 4 diarrhoea (24% vs 12%), which was most pronounced during the period of radiation. This study used a combination of bolus 5FU and FA in both arms. Leucopenia, stomatitis and vomiting were the next most common toxicities, with fewer than 10% of patients in either arm suffering from grade 3 or greater toxicity during the entire course of treatment.

Investigators from the much larger German trial, where completion of accrual occurred in November 2002, recently provided an updated progress report.[75] Significantly, the findings were very different to the NSABP R03 study and demonstrated reduced acute toxicity in the preoperative chemoradiotherapy setting. The principal toxicity was diarrhoea, with World Health Organization grade 3–4 diarrhoea in 9% of the preoperative arm vs 13% of the postoperative arm. Other acute toxicities, such as grade 3 nausea and vomiting, grade 3

erythema and grade 3 leucopenia, occurred in fewer patients who received preoperative chemoradiotherapy. An early report from the first 316 patients in the Polish trial,[71] which is comparing preoperative short-course radiotherapy and long-course chemoradiotherapy, found a reduced overall acute toxicity in patients who received radiotherapy alone (2% vs 17%).

In both NSABP R03[74] and the German study,[75] the incidence of postoperative complications, including postoperative bleeding, delayed wound healing, anastomotic leaks, SBO and fistula formation, was not increased after preoperative chemoradiotherapy.

Late adverse effects

Delayed adverse effects from combined-modality therapy have not been well documented as only a few RCTs have recently been completed. The late toxicity data are expected to become available in the next 3 years.

Preoperative short-course radiotherapy alone vs pre- and postoperative chemoradiotherapy

Our current practice is divided between these three options. While postoperative chemoradiotherapy for high-risk (T3–4 or N1) rectal cancer is the standard adjuvant therapy, there are several potential advantages with preoperative adjuvant therapy (radiotherapy alone or chemoradiotherapy). The rationale for this is improved patient compliance and, possibly, reduced toxicities. A comparison of the toxicities in contemporary studies using modern radiotherapeutic techniques is shown in Table 6.[1,2,5–13,38,58,59,61] The main difference between postoperative and preoperative adjuvant therapy is the lower incidence of acute gastrointestinal toxicity with preoperative adjuvant therapy. Preoperative short-course radiotherapy also causes less gastrointestinal toxicity than preoperative chemoradiotherapy. This is obviously not unexpected as the total dose of 25 Gy in five fractions is only biologically equivalent with late-reacting tissues. A large dose fraction produces relatively more damage to late-reacting than early-reacting tissues because of the differences in dose response kinetics. In order to avert potential toxicity in late-reacting tissues, the final dose of 25 Gy in five fractions was calculated to be biologically equivalent to 45 Gy delivered with conventional fractionation. With preoperative short-course radiotherapy, acutely reacting tissues such as skin and mucosal linings, and potentially the cancer itself, will be exposed to a total dose that is biologically lower than that delivered with preoperative long-course radiotherapy.[75] Concomitant administration of chemotherapy might potentiate the toxicity of the radiotherapy. There are no mature data from any trials comparing preoperative short-course radiotherapy and postoperative chemoradiotherapy, but a UKMRC trial comparing these two approaches is currently accruing patients.

However, preoperative short-course radiotherapy causes an increased incidence of perineal wound infection and breakdown compared with preoperative and postoperative chemoradiotherapy.[1,11,12,73,74] In addition, preoperative short-course radiotherapy does not cause down-staging of cancer and, hence, is unlikely to improve sphincter preservation. There is also an excess of cardiovascular events with preoperative short-course radiotherapy, most probably due to the larger fraction size delivered compared with long-course therapy.

Table 6. Comparison of mortality and morbidity with adjuvant therapy for rectal cancer

	Preoperative short-course radiotherapy	Preoperative chemoradiotherapy	Postoperative chemoradiotherapy
Mortality (%)	2–4	1.6–4	0–4
Morbidity (%)			
Diarrhoea	2	9–34	7–35
Nausea	NS	3–10	3–33
SBO/ileus	5–13	33–5	
Anastomotic leak	5–15	13	12
Wound infection	4–5	4	6
Perineal wound infection	20–26	NS	NS
Cardiovascular events	5	2	3

NS = not stated; SBO = small bowel obstruction.

Summary

The standard of care in rectal cancer has changed over the last few decades and will continue to evolve. Adjuvant therapy has improved the oncological outcome in high-risk (T3–4 or N1) rectal cancer. This benefit seems to be decreased with optimal surgery.[1,51] Any potential benefit of chemotherapy or radiotherapy ought to be balanced against the proven toxicities of adjuvant therapy. Documentation of therapeutic toxicity must be more stringent and should include tools to assess quality of life, as used in an Australian study.[76] Much effort has been expended to improve the planning and delivery of radiotherapy and chemotherapy to minimize morbidity. However, the future must involve a better selection of patients with high-risk rectal cancer who are more likely to benefit from adjuvant therapy, thus sparing others from unnecessary morbidity associated with adjuvant therapy.

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