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ORIGINAL REPORT

Randomized Trial of Short-Course Radiotherapy Versus Long-Course Chemoradiation Comparing Rates of Local Recurrence in Patients With T3 Rectal Cancer: Trans-Tasman Radiation Oncology Group Trial 01.04

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See accompanying editorial on page 3777

A B S T R A C T

Purpose

To compare the local recurrence (LR) rate between short-course (SC) and long-course (LC) neoadjuvant radiotherapy for rectal cancer.

Patients and Methods

Eligible patients had ultrasound- or magnetic resonance imaging–staged T3N0-2M0 rectal adenocarcinoma within 12 cm from anal verge. SC consisted of pelvic radiotherapy 5 × 5 Gy in 1 week, early surgery, and six courses of adjuvant chemotherapy. LC was 50.4 Gy, 1.8 Gy/fraction, in 5.5 weeks, with continuous infusional fluorouracil 225 mg/m^2 per day, surgery in 4 to 6 weeks, and four courses of chemotherapy.

Results

Three hundred twenty-six patients were randomly assigned; 163 patients to SC and 163 to LC. Median potential follow-up time was 5.9 years (range, 3.0 to 7.8 years). Three-year LR rates (cumulative incidence) were 7.5% for SC and 4.4% for LC (difference, 3.1%; 95% CI, −2.1 to 8.3; $P = .24$). For distal tumors (< 5 cm), six of 48 SC patients and one of 31 LC patients experienced local recurrence ($P = .21$). Five-year distant recurrence rates were 27% for SC and 30% for LC (log-rank $P = 0.92$; hazard ratio [HR] for LC:SC, 1.04; 95% CI, 0.69 to 1.56). Overall survival rates at 5 years were 74% for SC and 70% for LC (log-rank $P = 0.62$; HR, 1.12; 95% CI, 0.76 to 1.67). Late toxicity rates were not substantially different (Radiation Therapy Oncology Group/European Organisation for Research and Treatment of Cancer G3-4: SC, 5.8%; LC, 8.2%; $P = .53$).

Conclusion

Three-year LR rates between SC and LC were not statistically significantly different; the CI for the difference is consistent with either no clinically important difference or differences in favor of LC. LC may be more effective in reducing LR for distal tumors. No differences in rates of distant recurrence, relapse-free survival, overall survival, or late toxicity were detected.

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INTRODUCTION

Adding radiotherapy to surgery has been shown conclusively to improve local control for rectal cancer.[1,2] Short-course preoperative radiotherapy of 25 Gy in 5 consecutive days has been shown to be effective in tumor control. The Swedish Rectal Cancer Trial[3] demonstrated that short-course preoperative radiotherapy reduced the risk of local recurrence (LR) by half. In this study, improved overall survival was also evident. The Dutch Rectal Cancer Trial[4] demonstrated that short-course preoperative radiotherapy maintains its benefit when combined with the best surgical practice—total mesorectal excision. It was through meticulous study design and quality assurance that the value of short-course preoperative radiotherapy in addition to surgery was put beyond doubt. The MRC (Medical Research Council) CR07 rectal trial,[5] which compared short-course preoperative radiotherapy with selective postoperative chemoradiotherapy, provided further support for the short course approach.

Long-course preoperative chemoradiotherapy of 50.4 Gy in 5 weeks and 3 days with concurrent

chemotherapy has been widely practiced in the last 15 years. This regimen's superiority, in terms of local control, was demonstrated in the German rectal cancer trial,[6] when compared with postoperative chemoradiotherapy. The use of long-course preoperative chemoradiotherapy with different chemotherapeutic and biologic agents has been investigated with the aim of further improving local control and survival.[7,8]

Although both short-course preoperative radiotherapy and long-course preoperative chemoradiotherapy have been practiced in parallel for more than 15 years, it has not been clear which form of preoperative radiotherapy provides better tumor control. We performed a randomized trial for clinical stage T3 rectal cancer comparing short-course radiotherapy with long-course chemoradiotherapy. In this article, we report our results after a minimum follow-up period of 3 years, and we include the comparison of LR rates, relapse-free survival, overall survival, and late toxicity.

This trial was performed under the auspices of the Trans-Tasman Radiation Oncology Group, Australasian Gastro-Intestinal Trials Group, Colorectal Surgical Society of Australia and New Zealand, and The Royal Australasian College of Surgeons.

PATIENTS AND METHODS

The protocol was approved by the ethics committees of all participating centers. Written informed consent was obtained from each patient.

Patients

Eligible patients were those with histologically confirmed rectal adenocarcinoma, with lower borders within 12 cm of the anal verge; ultrasound- or magnetic resonance imaging (MRI) –staged T3 disease; Eastern Cooperative Oncology Group (ECOG) performance status 0 to 2; neutrophil count $\geq 1.5 \times 10^9$/L; platelet count $\geq 100 \times 10^9$/L; bilirubin and ALT ≤ 1.5 times the upper limit of normal; and serum creatinine ≤ 1.5 times the upper limit of normal. Exclusion criteria included evidence of distant metastases, recurrent rectal cancer, unstable cardiac disease, active infection, other cancers within 5 years, and prior radiotherapy. There was no restriction on nodal stage.

Study Design and Treatments

Eligible patients were randomly assigned to receive either short-course radiotherapy (SC) or long-course chemoradiotherapy (LC). SC comprised radiotherapy alone with a total of 25 Gy in five fractions administered in 1 week, followed by surgery 3 to 7 days later. Six monthly courses of fluorouracil (FU; 425 mg/m^2) and folinic acid (20 mg/m^2) administered daily for 5 days commenced 4 to 6 weeks after surgery.

LC chemoradiotherapy comprised a total of 50.4 Gy in 28 fractions over 5 weeks and 3 days with continuous infusional FU 225 mg/m^2 per day, administered 7 days per week for the duration of radiation. Surgery followed 4 to 6 weeks after chemoradiotherapy. Four monthly courses of the same chemotherapy as for SC patients commenced 4 to 6 weeks postsurgery.

The radiation clinical target volume (CTV) for SC was to include the primary rectal cancer, perirectal and internal iliac nodes, mesorectum, pelvic side walls, and presacral space with the upper border at the sacral promontory. The CTV for the initial phase of LC was identical to that for SC. The CTV was reduced after a total of 45 Gy to include gross disease with a 2-cm margin. Pelvic radiotherapy was administered using three- or four-field techniques. Treatment planning was performed with computerized dosimetry. Verification images were performed weekly.

Surgery was to be performed according to the Australian National Health and Medical Research Council guidelines.[9] Central pathology review was not a requirement.

Assessments

Before random assignment, patient assessment included sigmoidoscopy and biopsy, colonoscopy, computed tomography (CT) of the abdomen/pelvis, chest x-ray or CT, endorectal ultrasound or pelvic MRI, full blood examination, renal and liver function tests, carcinoembryonic antigen (CEA), and International Normalized Ratio. Enlarged nodes on staging were noted but nodal status was not an eligibility criterion.

Following completion of the protocol therapy, patient status was reviewed every 3 months for 24 months, then once every 6 months until 5 years postsurgery, then once a year thereafter. Liver function and CEA tests were performed at each visit. Late toxicity was assessed every 6 months for 24 months, then yearly until 5 years postsurgery, and was graded using the Radiation Therapy Oncology Group/European Organisation for Research and Treatment of Cancer Late Radiation Morbidity Scoring Scheme.[10]

End Points

LR was defined as recurrence within the true pelvis and either confirmed histologically or diagnosed from one or more of the following: progressive radiographic (CT or MRI) changes in a pelvic soft-tissue mass; progressive pelvic pain with radiographic changes; abnormally high uptake in the true pelvis on positron emission tomography scan; and visible or palpable tumor in the presence of distant metastasis. An independent review panel reviewed all recorded cases of LR. Recurrence outside the true pelvis was defined as distant.

Times to events were measured from random assignment or operation, as appropriate, and censored at the close-out date for analysis. The LR rate at a given time was defined as the cumulative incidence of LR (competing risks analysis with death as the other competing event). A similar definition applied to the distant-recurrence rate. Analysis of the competing risks of site of first recurrence and death was performed. Recurrence-free survival (RFS) was defined as time to recurrence or death, and overall survival (OS) as time to

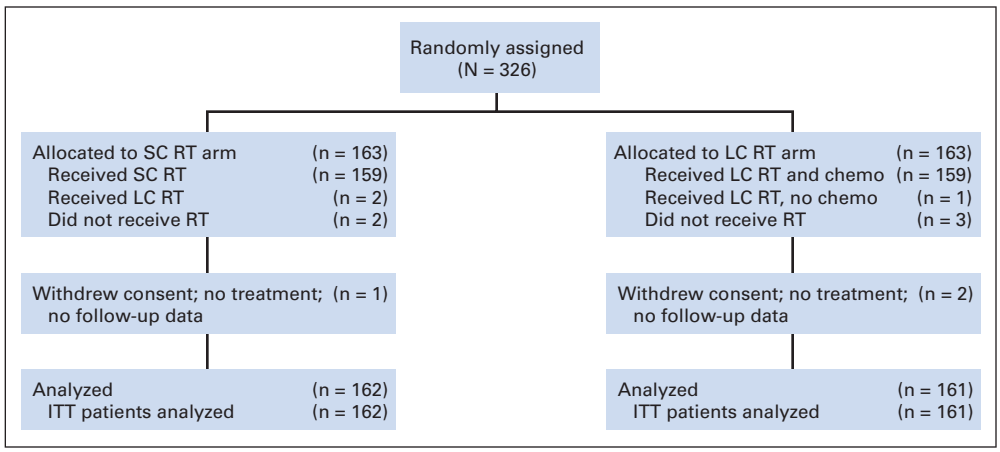

Fig 1. CONSORT diagram. Chemo, chemotherapy; ITT, intention-to-treat; LC, long course; RT, radiotherapy; SC, short course.

death from any cause. A closeout date was set at May 22, 2009, 3 years from the end of accrual. All data arising after this date were ignored to minimize reporting bias.

Statistical Analysis

The trial was designed to have 80% power to detect a difference in the primary end point, the LR rate at 3 years, of 15% (SC) versus 5% (LC)[11,12] using a two-sided test at the 5% level of significance. Three hundred ten evaluable patients, with a minimum follow-up of 3 years, were required. Patients were randomly assigned to study arms in a 1:1 ratio using an adaptive biased coin technique within strata corresponding to radiotherapy center. No specific early stopping rules were employed; in particular, there were no interim efficacy analyses, but there was ongoing monitoring of safety, data quality, protocol compliance, and accrual rate, including review by an Independent Data Monitoring Committee on four occasions during the accrual period.

LR rates were compared using their SEs as computed from the competing risks method and assuming approximate normality. The primary analysis was unadjusted and based on the intention-to-treat principle, namely that all eligible and evaluable patients were included in the analysis and analyzed according to the arm to which they were assigned. Subsidiary analyses included Gray's test for comparing cumulative incidence curves and analyses adjusting for prognostic variables.

Secondary aims compared treatments with respect to time to LR, time to distant recurrence, RFS, and OS via log-rank and Cox regression methods. Log-rank tests were exact, being based on hypergeometric probabilities. RFS and OS curves were estimated using the Kaplan-Meier method. *P* values from contingency tables were exact. Analyses of prognostic factors including sex, age, ECOG performance status (0 *v* 1-2), node positivity, distance from anal verge (continuous), (log) CEA, and treatment arm, with multiple imputation of missing values[13] for node status and CEA; also margin positivity (macroscopic or microscopic), ypT, and ypN were included in analysis at operation, and were performed using backward elimination. Late toxicity rates (crude) were tabulated by type and compared by arm. Important end points were calculated using 95% CIs and *P* values were two-sided. Analyses were performed using the *R* statistical language (http://www.R-project.org).

RESULTS

Twenty-seven centers in Australia and New Zealand contributed patients from 2001 to 2006; 326 patients were randomly assigned, 163 to each arm (Fig 1). Three patients withdrew completely from the trial before treatment and were excluded, leaving 323 patients for analysis (SC, 162; LC, 161). The median potential follow-up time was 5.9 years and, for patients not lost to follow-up, ranged from 3.0 to 7.8 years. Eleven patients (SC, 6; LC, 5) with incomplete follow-up had a median follow-up time of 3.5 years (range, 0.9 to 6.0). Table 1 lists distributions of patient characteristics between study arms. These seem well-balanced except for distance from anal verge, which tends to be shorter in SC patients (30% $<$ 5 cm compared with 19% of LC patients).

All patients administered SC received a total of 25 Gy; of patients administered LC, 93% received a total of 50.4 Gy, and 84% of patients received concurrent FU within 10% of the planned dose. Adjuvant chemotherapy was delivered to 85% of SC and 86% of LC patients. Reasons for not receiving adjuvant chemotherapy were health-related issues (61% of patients), patient decision (24%), and clinician decision (15%).

Table 1. Patient Characteristics by Arm

Characteristic	SC (n = 162) No. of Patients	SC (n = 162) %	LC (n = 161) No. of Patients	LC (n = 161) %
Sex				
Male	117	72	120	75
Female	45	28	41	25
Age at random assignment, years				
Median	63		64	
Range	26 to 80		29 to 82	
ECOG performance status				
0	102	63	87	54
1	59	36	71	44
2	1	1	3	2
T3 stage	162	100	161	100
N stage				
0	91	56	90	56
1	59	36	59	37
2	1	1	2	1
X	11	7	10	6
M0 stage	162	100	161	100
CEA, ng/ml				
Median	3.0		3.0	
Range	0.2 to 375		0.10 to 304	
Missing	16		8	
Staging investigations				
MRI staged	49	30	51	32
Ultrasound staged	84	52	81	50
MRI plus ultrasound	20	12	17	11
CT staged	9	6	12	7
Distance of lower border from anal verge, cm				
0 to $<$ 5	48	30	31	19
$\geq$ 5 to $<$ 10	88	54	88	55
$\geq$ 10 to 12	26	16	42	26
Mean	6.2		7.0	
Range	0 to 12		0 to 12	

Abbreviations: CEA, carcinoembryonic antigen; CT, computed tomography; ECOG, Eastern Cooperative Oncology Group; LC, long course; MRI, magnetic resonance imaging; SC, short course.

Local Recurrence

Twenty-one patients experienced LR as a first or subsequent recurrence (SC, 12; LC, 9), and 79 died without prior LR (SC, 35; LC, 44). Cumulative incidences of LR at 3 years were 7.5% for SC (SE, 2.1%) and 4.4% for LC (SE, 1.6%; difference, 3.1%; 95% CI, −2.1% to 8.3%; $P = 0.24$). Cumulative incidence curves of LR were not statistically different (Gray's test $P = .49$; Fig 2A). Cumulative incidences of LR at 5 years were 7.5% for SC (SE, 2.1%) and 5.7% for LC (SE, 1.8%; difference, 1.8%; 95% CI, −3.6% to 7.3%; $P = 0.51$).

The observed risk of LR (log-rank analysis) was smaller for LC but not statistically significant (HR for LC:SC, 0.75; 95% CI, 0.32 to 1.77; $P = .66$). Thirteen patients experienced LR as a first recurrence; the observed risk was less for LC but not statistically significantly so (HR for LC:SC, 0.64; 95% CI, 0.22 to 1.89; $P = .58$).

Prognostic Factors at Baseline for Local Recurrence

Age, ECOG performance status, node positivity, and CEA were significant determinants of LR in univariable analyses. In multivariable analysis of the seven factors considered (see Statistical Analysis), only CEA was statistically significant (HR, 1.43; per doubling, $P = .001$).

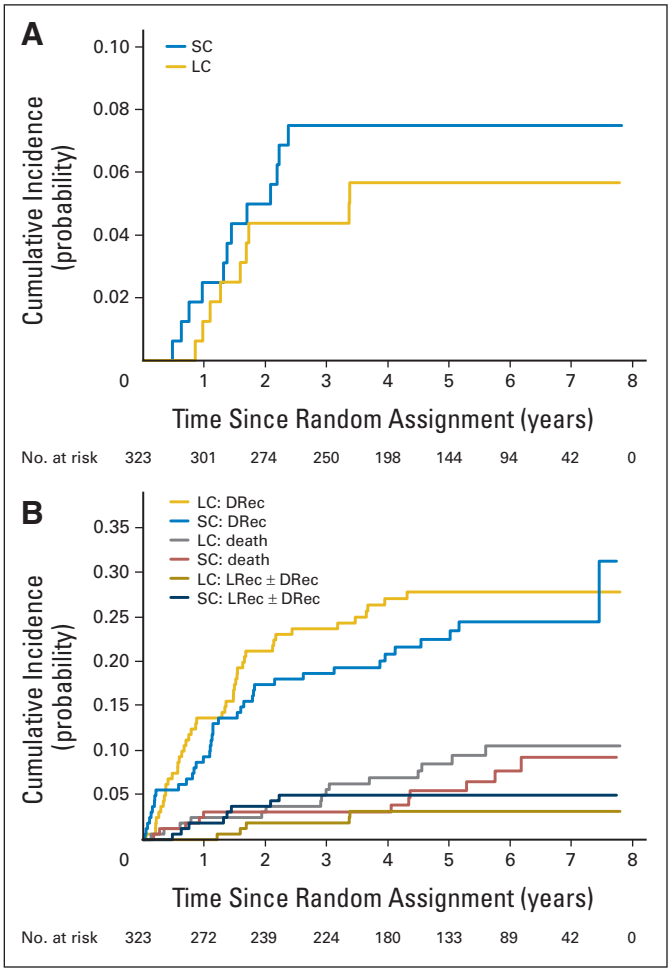

Fig 2. (A) Cumulative incidence curves of any local recurrence (LRec) by allocated treatment arm: competing risks analysis for events, LRec, and death (not shown). (B) Cumulative incidence curves of first relapse site (local—with or without simultaneous distant—or distant alone) and death by allocated treatment arm: competing risks analysis for events, local recurrence with or without simultaneous distant recurrence (LRec ± DRec), distant recurrence (DRec) only, and death. LC, long course; SC, short course.

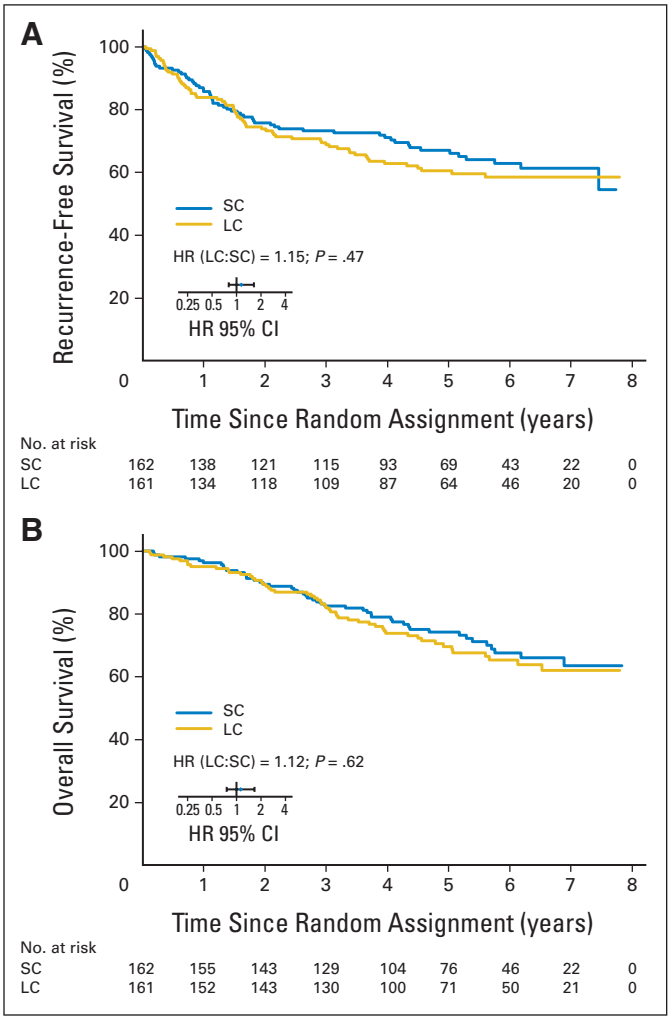

Fig 3. (A) Recurrence-free survival curves by allocated treatment arm. (B) Overall survival curves by allocated treatment arm. HR, hazard ratio; LC, long course; SC, short course.

Relapse and Survival

Sites of first relapse by arm are listed in Table 2. Figure 2B shows cumulative incidence curves by site of first recurrence (local and/or distant) and death without recurrence and by treatment arm.

Table 2. First Relapse Site Combinations by Arm

Sites of First Recurrence	SC	LC	Total
Local only	4	4	8
Distant only	38	44	82
Local and distant	4	1	5
Death without prior recurrence	11	15	26
Total No. of patients with recurrence	46	49	95
Total No. of patients who recurred or died	57	64	121
No recurrence or death	105	97	202
Total	162	161	323

Abbreviations: SC, short course; LC, long course.

Ninety-three patients (SC, 46; LC, 47) experienced a distant recurrence either as a first or subsequent recurrence. Five-year cumulative incidence rates of distant recurrence were 27% and 30% for SC and LC, respectively (Gray's test $P = .89$). There were no apparent differences in relative risks of distant recurrence (log-rank $P = .92$; HR for LC:SC, 1.04; 95% CI, 0.69 to 1.56).

Relapse or death was experienced by 121 patients (SC, 57; LC, 64), with no difference in RFS between arms (HR for LC:SC, 1.15; 95% CI, 0.80 to 1.62; $P = .47$; Figure 3A). Ninety-nine patients died (SC, 47; LC, 52), including 21 patients of causes unrelated to rectal cancer or its treatment. There was no difference demonstrated in OS between arms (5-year OS rates: SC, 74%; LC, 70%; HR for LC:SC, 1.12; 95% CI, 0.76 to 1.67; $P = .62$; Figure 3B).

Operative Findings

Five of the 323 patients did not receive the allocated treatment (ie, SC or LC plus preoperative chemotherapy) and three patients did not proceed to surgery. Operative findings of the remaining 315 patients (SC, 158; LC, 157) are summarized in Table 3. The table of surgical complications is summarized in Appendix Table A1 (online only).

Table 3. Operative Findings by Arm

Factor	SC No. of Patients	SC %	LC No. of Patients	LC %	*P*
Distance of lower border from anal verge at baseline, cm					.017*
0 to < 5	48	30	30	19	
≥ 5 to < 10	86	54	87	55	
≥ 10 to 12	24	15	40	25	
Macroscopic resection					
Complete	154	97	153	97	
Incomplete	4	3	4	3	
Margin status†					
Negative	150	95	151	96	
Positive	8	5	6	4	
ypT					< .001‡
0	2	1	24	15	
1	7	4	4	3	
2	35	22	43	27	
3	106	67	82	52	
4	8	5	4	3	
T downstaging					.003§
Downstaged, ypT0-2	44	28	71	45	.002¶
Unchanged, ypT3	106	67	82	52	
Upstaged, ypT4	8	5	4	3	
ypN					.50*
0	95	60	102	65	
1	39	25	40	25	
2	24	15	15	10	
Grade, resection specimen					.056‖
WD	3	2	7	6	
MWD	100	66	93	74	
PD/UD	28	18	18	14	
Mixed	21	14	8	6	
Unknown	4		8		
N/A (CR)	2		23		
Type of operation					.22
APR	59	37	48	31	
non-APR	99	63	109	69	

NOTE. For 315 patients who received the allocated preoperative treatment and proceeded to surgery. Data include 13 patients with major eligibility infringements (n = 2) or who had distant metastasis detected before or at operation (n = 11).

Abbreviations: APR, abdominoperineal resection; LC, long course; MWD, moderately well differentiated; N/A (CR), not applicable (complete response); PD, poorly differentiated; SC, short course; UD, undifferentiated; WD, well differentiated.

*$df = 2$.

†Twelve circumferential and two distal.

‡$df = 4$.

§P for trend; $df = 2$.

¶P for T0-2 *v* T3-4.

‖$df = 3$.

Pathologic downstaging was significantly more common in patients randomly assigned to LC (45% *v* 28%; $P = .002$). In particular, 24 LC patients (15%) had a pathologic complete response (ypT0) compared with two SC patients (1%). In patients with distal tumors (< 5 cm), the abdominoperineal resection (APR) rates were 79% (38 of 48 patients) and 77% (23 of 30 patients) for SC and LC, respectively ($P = .87$).

Prognostic Factors at Operation for Local Recurrence

Patients with major eligibility infringements (two patients), major protocol violations (five patients), no operation (three patients), and distant metastasis detected before or at operation (11 patients) were excluded, leaving 302 patients for analysis (SC, 153; LC, 149). Patients analyzed include eight with macroscopically incompletely resected tumors and eight whose resected tumors had a positive resection margin. In multivariable analysis, of the 10 factors considered (see Statistical Considerations) margin positivity (macro- or microscopic; HR, 6.46; $P < .001$), ypN positivity (HR, 3.56; $P < .001$), and baseline CEA (HR, 1.32; per doubling, $P = .033$) were independently prognostic. For patients on LC, none of 20 pathologic complete response (pCR) patients recurred locally compared with nine of 129 non-pCR patients ($P = .38$).

Distance From Anal Verge

When the whole cohort of 323 patients was analyzed, distance from anal verge was not significantly related to risk of LR either as a continuous covariate (univariate $P = .25$; adjusting for arm $P = .29$) or comparing distal (< 5 cm) and proximal tumors (seven of 79 *v* 14 of 244, respectively; HR for distal:proximal, 1.59; 95% CI, 0.58 to 4.34; log-rank $P = 0.31$). There was no statistical evidence for a differential effect of treatment on risk of LR according to distance from anal verge (interaction $P = 0.24$).

For 79 distal tumors there was a large, observed (but not statistically significant) difference between treatments with respect to risk of LR, with six of 48 patients on SC and one of 31 patients on LC experiencing local recurrence (HR for LC:SC, 0.26; 95% CI, 0.06 to 1.20; $P = .26$). The cumulative incidences of local recurrence were 12.5% for SC (SE, 4.8%) and 0.0% for LC (SE, 0.0). A comparison of the crude proportions (SC, six of 48; LC, one of 31) gave $P = .21$. Of the 302 patients defined in the Prognostic Factors at Operation for Local Recurrence section, similar results were obtained from analyses of data from 103 patients who had an APR and 58 of these 103 patients who had distal tumors.

Late Toxicity

Radiation Therapy Oncology Group/European Organisation for Research and Treatment of Cancer late radiation toxicities are listed in Table 4. The rates for G3-4, small or large intestine toxicity for SC and

Table 4. Late RT Toxicities by Worst Grade

Late RT Toxicity Type	SC (n = 155) Grade 3	SC (n = 155) Grade 4	LC (n = 158) Grade 3	LC (n = 158) Grade 4
Skin, pelvic	0	1	0	1
Subcutaneous tissue	0	1	0	1
Small or large intestine	2	3	6	2
Bladder	3	0	2	0
Other*	2	1	3	0
Any toxicity	6	3	10	3

NOTE. The maximum grade (RTOG/EORTC Late Radiation Morbidity Scoring Scheme) for each type and each patient was determined. Only grades 3 or 4 late toxicities are tabulated. Of the total number of patients evaluable for late RT toxicity analysis, 155 patients received SC and 158 patients received LC.

Abbreviations: EORTC, European Organisation for Research and Treatment of Cancer; LC, long course; RT, radiotherapy; RTOG, Radiation Therapy Oncology Group; SC, short course.

*Other reported toxicities for SC included vesicocutaneous fistula (grade 4), anastomotic stricture requiring dilatations (grade 3), and proctalgia (grade 3). Other toxicities for LC included deep venous thrombosis (grade 3), perianal pain (grade 3), and presacral abscess (grade 3). The crude rates of late RT toxicity were 5.8% (nine of 155 patients) for SC and 8.2% (13 of 158 patients) for LC ($P = .53$).

LC were 3.2% and 5.1%, respectively (difference for LC-SC, 1.8%; 95% CI, −3.0% to 6.9%; $P = .53$). The crude rates of any late grade 3 to 4 RT toxicity were 5.8% for SC (nine of 155) and 8.2% for LC (13 of 158; difference for LC-SC, 2.4%; 95% CI, −3.6% to 8.5%; $P = .53$) and were not substantially different between arms.

DISCUSSION

This trial included only ultrasound- or MRI-staged, advanced cancers (cT3) and those with the lower edge of tumor in the lower two-thirds of the rectum. In 6.5% of patients, CT evidence of perirectal fat infiltration was accepted after unsuccessful endorectal ultrasound (so that bulky or stenotic T3 lesions were not excluded). For the short-course arm of the Dutch trial[14] stage I, II, and III disease was included and adjuvant chemotherapy was not used; our trial included only clinical T3 disease and adjuvant chemotherapy was standardized in the protocol. The Polish trial[15] differed from ours in that concurrent chemotherapy administered during chemoradiotherapy was bolus FU and leucovorin, adjuvant chemotherapy was optional, endorectal ultrasound or MRI was not performed for all patients but was reserved for mobile lesions, and all circular or tethered lesions on digital rectal examination were determined as T3 or T4 tumors.

We demonstrated a small difference in the LR rate at 3 years, 3.1%, favoring LC ($P = .24$). The 95% CI for the difference (SC-LC: 95% CI, −2.1% to 8.3%) includes differences of 8% or more in favor of LC (eg, 10% *v* 2%) so the trial has not excluded there being a clinically important difference in 3-year LR rates. The data are consistent with either no difference or an important clinical difference in favor of LC; it's unlikely that there is an important difference favoring SC. In the Polish trial,[16] there was no statistically significant difference in LR rate between SC and LC preoperative radiotherapy, although the trend favored SC (4-year LR rates: SC, 10.6%; LC, 15.6%; $P = .21$; inferred 95% CI for SC-LC approximately −11.3% to 1.3%). Results in the two trials are consistent with no true difference in LR rates, although differences between arms are in opposite directions. However, because of the trials' different stage profiles it is difficult to make a valid comparison.

We did not find a statistically significant difference in LR risk between treatments for distal cancer (< 5 cm), despite there being a large observed difference favoring LC (six of 48 SC patients *v* one of 31 LC patients recurred locally). This trend is consistent with the common belief that LC is superior for distal T3 disease. It is also consistent with Dutch trial results in which SC for distal disease was relatively ineffective.[14]

Aspects of treatment other than radiotherapy in our trial, such as the intensity of chemotherapy, were well balanced between the arms. As there was no significant difference in LR between study arms, it was not surprising that there were no significant differences in RFS or OS.

After surgery, positive resection margin, involved lymph nodes in the resected specimen, and baseline CEA were independently associated with LR. Caution is required with interpretation because of the small number of events analyzed; nevertheless, the results affirm the importance of resection margins, lymph node involvement, and CEA level in LR.

We observed, as expected, that there was a greater pathologic T and N downstaging effect with LC. However, there was no apparent effect on APR rate for distal tumors (79% *v* 77%). Similarly, the Polish trial did not find that long-course chemoradiotherapy reduced APR rate.[15] It may be that downsizing was not sufficient to alter the surgical approach, or there was concern about residual microscopic disease even after a good response, or surgeons made their clinical decision based on the pretherapy distal margin rather than perioperative clinical response to radiotherapy. SC with early surgery does not allow enough time for the tumor to regress, and so a reduction in APR rate would not be expected. The effect of delayed surgery for SC will be addressed by the Stockholm III trial.[17]

There is still some concern that late toxicity from hypofractionated SC radiotherapy may exceed that for fully fractionated LC. We observed no significant difference in severe late toxicity at 3 years and, in particular, no reports of severe neuropathy.[18] Longer follow-up is required to fully assess late effects. Analysis of quality of life data is planned to be performed after 5 years. Longer follow-up is also being planned for local recurrence, as well as distant recurrence and survival.

The trial data indicate that LC may be more effective than SC in reducing the risk of LR, especially for distal tumors. However, we have not been able to definitively determine that such a difference does exist, and further study would be required to help clarify this issue. At this stage of study, it may be reasonable to suggest a policy that distal or bulky tumors be treated with LC, and that where convenience is an important consideration SC be used.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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