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ORIGINAL ARTICLE

Organ preservation after neoadjuvant long-course chemoradiotherapy versus short-course radiotherapy

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Background: Potential differences in organ preservation between total neoadjuvant therapy (TNT) regimens integrating long-course chemoradiotherapy (LCCRT) and short-course radiotherapy (SCRT) in rectal cancer remain undefined.

Patients and methods: This natural experiment arose from a policy change in response to the COVID-19 pandemic during which our institution switched from uniformly treating patients with LCCRT to mandating that all patients be treated with SCRT. Our study includes 323 locally advanced rectal adenocarcinoma patients treated with LCCRT-based or SCRT-based TNT from January 2018 to January 2021. Patients who achieved clinical complete response were offered organ preservation with watch-and-wait (WW) management. The primary outcome was 2-year organ preservation. Additional outcomes included local regrowth, distant recurrence, disease-free survival (DFS), and overall survival (OS).

Results: Patient and tumor characteristics were similar between LCCRT ($n = 247$) and SCRT ($n = 76$) cohorts. Median follow-up was 31 months. Similar clinical complete response rates were observed following LCCRT and SCRT (44.5% versus 43.4%). Two-year organ preservation was 40% [95% confidence interval (CI) 34% to 46%] and 31% (95% CI 22% to 44%) among all patients treated with LCCRT and SCRT, respectively. In patients managed with WW, LCCRT resulted in higher 2-year organ preservation (89% LCCRT, 95% CI 83% to 95% versus 70% SCRT, 95% CI 55% to 90%; $P = 0.005$) and lower 2-year local regrowth (19% LCCRT, 95% CI 11% to 26% versus 36% SCRT, 95% CI 16% to 52%; $P = 0.072$) compared with SCRT. The 2-year distant recurrence (10% versus 6%), DFS (90% versus 90%), and OS (99% versus 100%) were similar between WW patients treated with LCCRT and SCRT, respectively.

Conclusions: While WW eligibility was similar between cohorts, WW patients treated with LCCRT had higher 2-year organ preservation and lower local regrowth than those treated with SCRT, yet similar DFS and OS. These data support induction LCCRT followed by consolidation chemotherapy as the preferred TNT regimen for patients with locally advanced rectal cancer pursuing organ preservation.

Key words: rectal cancer, organ preservation, long-course chemoradiotherapy, short-course radiotherapy, local regrowth, natural experiment

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INTRODUCTION

The rapid rise in the incidence of rectal cancer, especially among young adults,[1] has spurred interest in treatment de-intensification strategies that include organ preservation for selected candidates who achieve a clinical complete response (cCR) to total neoadjuvant therapy (TNT).[2-4] In the context of organ preservation, potential differences between TNT regimens integrating long-course chemoradiotherapy (LCCRT) and short-course radiotherapy (SCRT) have not been delineated. While multiple prospective studies comparing LCCRT and SCRT have shown similar oncological outcomes (Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2024.07.729), these studies were limited in that all patients proceeded to surgery without the opportunity to be considered for watch-and-wait (WW) surveillance.[5-13] Although the National Comprehensive Cancer Network (NCCN) recognizes both LCCRT and SCRT as acceptable neoadjuvant treatment strategies to facilitate organ preservation,[14] it is unknown whether TNT regimens integrating LCCRT and SCRT yield similar rates of organ preservation. Most organ preservation studies to date have utilized LCCRT (Supplementary Table S2, available at https://doi.org/10.1016/j.annonc.2024.07.729).[2-4,15-25] While SCRT has advantages over LCCRT in terms of cost and convenience,[26,27] the oncological efficacy of SCRT-based TNT regimens to facilitate organ preservation relative to LCCRT-based TNT regimens remains unclear.

During the peak of the COVID-19 pandemic, the Memorial Sloan Kettering (MSK) Cancer Center Colorectal (CRC) Disease Management Team (DMT) mandated the use of SCRT instead of LCCRT to ensure uninterrupted oncological care while minimizing viral exposure to both patients and staff.[28] This approach aimed to mitigate chemotherapy-induced immunosuppression by omitting concurrent chemotherapy and to reduce health care resource utilization.[28,29] This policy created a natural experiment to compare the oncological efficacy of organ preservation in rectal cancer patients treated uniformly with SCRT-based TNT versus those treated with standard LCCRT-based TNT.

METHODS

Study design and participants

This study was approved by the MSK Institutional Review Board (IRB 16-370) with a waiver of informed consent. Medical records were reviewed to identify patients with biopsy-proven, locally advanced rectal adenocarcinoma who received TNT from January 2018 to January 2021. Data were collected through medical record review from inpatient and outpatient visits at our institution, as well as from available records from outside health care providers. Patient characteristics and clinicopathologic data were collected, including age at diagnosis, patient-reported sex, patient-reported race and ethnicity, pathology, clinical tumor and nodal staging, neoadjuvant treatment regimen, post-treatment response, and surgical procedures. Exclusion criteria included clinical stage IV disease, metachronous or synchronous cancers diagnosed within the past 5 years, non-adenocarcinoma pathology, insufficient radiation data, upfront radical surgery, prior pelvic radiation, receipt of SCRT outside of the pandemic-related mandate periods, and progression of disease while on TNT, as summarized in Figure 1.

Work-up included examination by a radiation oncologist, medical oncologist, and/or colorectal surgeon, including digital rectal examination (DRE), endoscopy (anoscopy or flexible sigmoidoscopy), routine blood work, and diagnostic imaging [staging computed tomography (CT) of the chest, abdomen, and pelvis and magnetic resonance imaging (MRI) of the rectum]. All patients were staged according to the American Joint Committee on Cancer (AJCC) eight edition.[30] Tumor mutational profiling was carried out with Integrated Mutational Profiling of Actionable Cancer Targets (MSK-IMPACT), as previously described.[31]

Neoadjuvant therapy

During the institutional COVID-19 mandate periods, all patients with locally advanced rectal cancer were treated with SCRT [2500 centigray (cGy) in 500 cGy fractions over consecutive weekdays] between March 2020 and June 2020 and between November 2020 and January 2021. No exceptions were allowed during these mandate periods. It was preferred, but not mandated, to initiate SCRT on Monday to allow all five fractions to be administered consecutively without a break. Five patients treated with SCRT outside of the mandate periods were excluded (Figure 1). Three-dimensional conformal radiotherapy (3DCRT) and intensity-modulated radiotherapy (IMRT) were permitted.

During the peri-mandate periods (i.e. between January 2018 and February 2020 and between July 2020 and October 2020), patients were treated with LCCRT as previously described.[3,4,32] Briefly, patients treated with 3DCRT received 4500 cGy in 25 fractions of 180 cGy followed by a sequential boost to gross disease, reaching a total dose of 5040-5400 cGy in 28-30 fractions. Patients treated with IMRT received 4698 cGy in 27 fractions of 174 cGy with a simultaneous integrated boost to 5400 cGy in 27 fractions of 200 cGy, or they received 4500 cGy in 25 fractions of 180 cGy with a simultaneous integrated boost to gross disease to 5000 cGy in 25 fractions of 200 cGy followed by a sequential boost to gross disease to a total dose of 5400 cGy in 27 fractions. All patients were evaluated weekly by the treating radiation oncologist during radiation treatment using a standardized toxicity assessment that integrated the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 5.0.[33]

All patients were treated with induction or consolidation chemotherapy, at the discretion of the treating physicians. Standard systemic chemotherapy regimens included CAPOX (capecitabine and oxaliplatin) or FOLFOX (fluorouracil, leucovorin, and oxaliplatin), as previously described.[3,4,32] During chemotherapy, patients were evaluated at each cycle by the treating medical oncologist. Generally, there was a

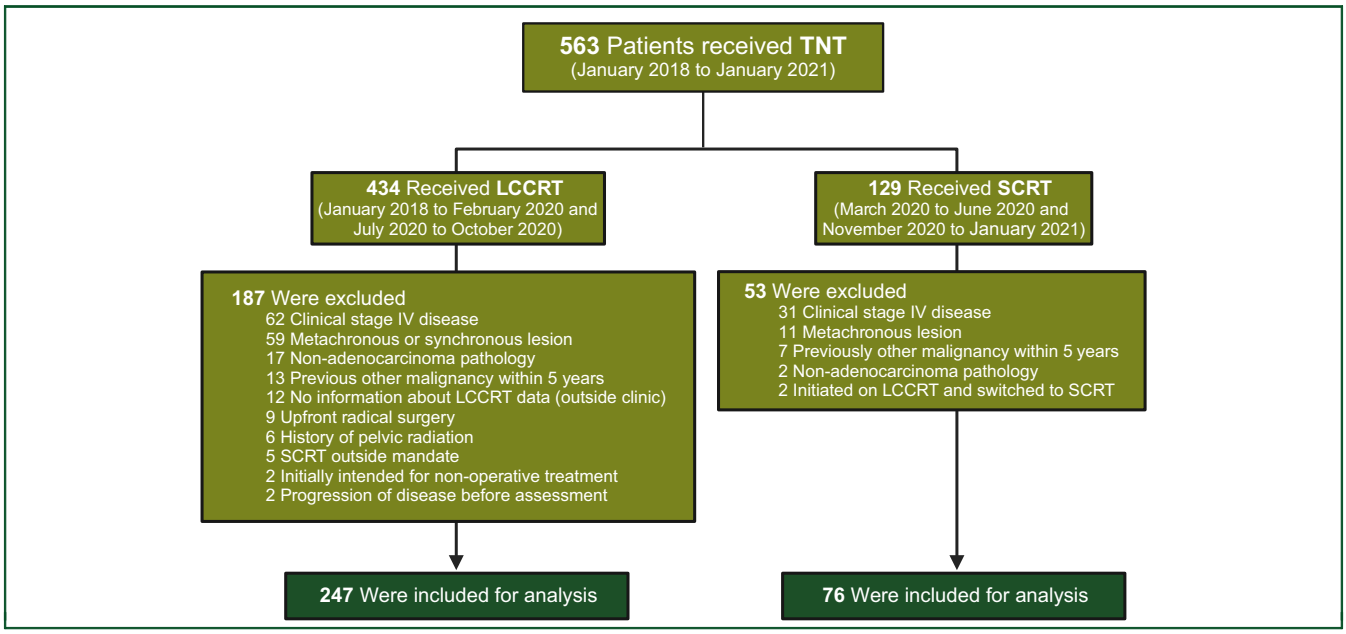

Figure 1. Patient review and selection criteria.
LCCRT, long-course chemoradiotherapy; SCRT, short-course radiotherapy; TNT, total neoadjuvant therapy.

4-week treatment-free interval between induction and consolidation therapies, irrespective of the sequence of treatments [i.e. induction (chemo)radiation followed by consolidation chemotherapy versus induction chemotherapy followed by consolidation (chemo)radiation].

Clinical response

Approximately 8 weeks following the completion of TNT, patients underwent response assessment via clinical exam, endoscopy, and rectal MRI. The final assessment of clinical response, as defined by the MSK rectal cancer regression schema, was based on the clinical judgment of the treating physicians in collaboration with the MSK CRC DMT.[14,32] Patients with a cCR were considered WW eligible. Patients with a near-complete response (nCR) were recommended to undergo a clinical and radiographic re-evaluation in 6-12 weeks to allow additional time for the treatment response to mature.[14] Patients with nCR who subsequently achieved cCR were considered WW eligible, while those who failed to evolve to cCR were deemed to be incomplete responders (non-cCR). All WW eligible patients were informed of the risks, benefits, and alternatives to nonoperative management. WW eligible patients who agreed to the requisite follow-up assessments entered WW management. Surgery [i.e. total mesorectal excision (TME)] was recommended for all patients who did not achieve cCR and for patients who declined WW management.

Treatment response monitoring

Surveillance for WW patients was per standard of care,[14] which generally included a physical evaluation including DRE, endoscopy, and laboratory tests including carcinoembryonic antigen (CEA) every 4 months for 2 years and then every 6 months up to year five. In addition, a rectal MRI was generally obtained every 4-6 months for up to 3 years after completing treatment, and a chest, abdomen, and pelvis CT was generally obtained every 6-12 months for a total of 5 years after completing treatment. Patients who underwent TME were followed with physical evaluation and laboratory tests, including CEA every 4 months for 2 years and then every 6 months up to year 5 and including a chest, abdomen, and pelvis CT generally obtained every 6-12 months for 5 years after completing treatment.

Patient-reported quality of life

Patient-reported questionnaires were integrated into routine clinical practice, and bowel function was assessed using the validated low anterior resection syndrome questionnaire (LARS-Q).[34] Patients were asked to complete the LARS-Q (Supplementary Figure S1, available at https://doi.org/10.1016/j.annonc.2024.07.729) at baseline and at 6 months and 12 months following TNT completion.

Outcomes

The primary outcome was 2-year organ preservation. Organ preservation time was defined as the time from the date of TNT completion to the date of the first occurrence of the following events: TME carried out or attempted, local regrowth after an initial apparent clinical and radiological complete response that could not be resected with an R0 TME, and death due to all causes. Patients with local regrowth amenable to salvage by transanal excision (TAE) were considered to have maintained organ preservation. Secondary endpoints included 2-year local regrowth, distant recurrence, disease-free survival (DFS), and overall survival (OS) rates. Local regrowth was defined as any evidence of pelvic tumor reappearance on WW surveillance following the confirmation of cCR. DFS was defined as the time from date of

TNT initiation to the date of the first occurrence of the following events: death due to all causes, pelvic tumor recurrence after TME, local regrowth after an initial apparent clinical and radiological complete response that could not be resected with an R0 TME, and diagnosis of metastatic disease at any point after initiation of treatment. Of note, any local regrowth amenable to salvage with an R0 TME was not considered to be a DFS event, as previously reported.[3,35] OS was calculated from the date of TNT initiation until the date of death from any cause. For salvage surgery patients, all outcomes were calculated from the date of salvage surgery. TNT start dates for two patients and TNT completion dates for three patients were used based on median lengths of TNT given a patients' sequence of treatment and cohort.

Statistical analysis

Patient demographics and tumor characteristics were summarized using median and interquartile range (IQR) for continuous covariates and percentages for categorical covariates. Comparison of percentages between groups were carried out using two-sided Fisher's exact or Pearson's Chi-square tests. The Wilcoxon rank sum test was carried out to compare medians between groups. A P value <0.05 was considered statistically significant. Median follow-up time was estimated using the reverse Kaplan—Meier method. The Kaplan-Meier method was used to estimate organ preservation, local regrowth, distant recurrence, and survival (i.e. DFS, OS) at 2-year endpoint, with log-rank test to assess for differences between survival curves. For tumor mutational profiling analysis, differences in gene frequencies were assessed with the Fisher's exact test. All statistical analyses were carried out using R 4.2.2.

RESULTS

Patient and tumor characteristics

Five hundred and sixty-three consecutive patients with rectal adenocarcinoma were treated with TNT from January 2018 to January 2021, of whom 323 patients met study eligibility (LCCRT = 247 and SCRT = 76) (Figure 1). The LCCRT and SCRT cohorts did not differ in baseline patient and tumor characteristics (Table 1). Among the 160 patients (122 LCCRT and 38 SCRT) with pretreatment genetic profiling data, a lower frequency of SMAD4 and SOX9 alterations was observed in the LCCRT cohort compared with the SCRT cohort (Supplementary Figure S2, available at https://doi.org/10.1016/j.annonc.2024.07.729). The median follow-up was 31 months [95% confidence interval (CI) 30-32 months], with a slightly longer follow-up for patients treated with LCCRT (32 months; 95% CI 31-34 months) compared with SCRT (28 months; 95% CI 26-29 months).

Treatment characteristics

Treatment characteristics are reported in Table 2. Most patients were treated with induction chemotherapy followed by consolidation chemoradiation (77% for LCCRT versus 70% for SCRT). For these patients, there was no difference in the interval between the completion of chemotherapy and initiation of chemoradiation [median (IQR), 3.9 weeks (2.7-5.0 weeks) for LCCRT versus 4.4 weeks (3.4-5.7 weeks) for SCRT; $P = 0.064$]. For patients treated with induction chemoradiation followed by consolidation chemotherapy, however, the interval between the completion of chemoradiation and initiation of chemotherapy was longer with LCCRT compared with SCRT [median (IQR), 5.4 weeks (3.5-9.1 weeks) for LCCRT versus 3.6 weeks (2.4-4.4 weeks) for SCRT; $P = 0.004$]. The overall duration of TNT was longer for patients treated with LCCRT compared with SCRT [median (IQR), 23.5 weeks (21.9-25.2 weeks) for LCCRT versus 18.8 (16.0-20.3 weeks) for SCRT; $P < 0.001$].

Most patients were treated with IMRT (61% for LCCRT versus 74% for SCRT) (Table 2). The median treatment dose was 5400 cGy (IQR 5010-5400 cGy) in the LCCRT cohort and 2500 cGy (IQR 2500-2500 cGy) in the SCRT cohort (Table 2). Most patients received FOLFOX or CAPOX chemotherapy (96.4% for LCCRT and 98.7% for SCRT) (Table 2). The duration of systemic chemotherapy was similar [median (IQR), 14.0 weeks (13.7-15.0 weeks) for LCCRT versus 14.0 weeks (10.8-15.0 weeks) for SCRT; $P = 0.072$], between cohorts (Table 2 and Supplementary Figure S3, available at https://doi.org/10.1016/j.annonc.2024.07.729).

The median interval from completion of TNT to initial restaging was similar between cohorts: 8.0 weeks (IQR 6.0-10.3 weeks) for LCCRT versus 9.0 weeks (IQR 7.3-10.7 weeks) for SCRT. For patients who achieved cCR upon initial assessment, the median intervals from completion of TNT to date of cCR were similar: 8.1 weeks (IQR 6.6-10.1 weeks) for LCCRT and 9.1 weeks (IQR 7.3-10.6 weeks) for SCRT. For patients who evolved from nCR to cCR, the median intervals from completion of TNT to date of cCR were also similar: 20.4 weeks (IQR 16.3-25.9 weeks) for LCCRT and 18.9 weeks (IQR 18.0-19.7 weeks) for SCRT. Two patients (1%) died during TNT in the LCCRT cohort, and one patient (1%) died during TNT in the SCRT cohort.

LCCRT-WW cohort

Among the 247 patients treated with LCCRT, 110 (44.5%) patients achieved cCR and were eligible for WW management. This included 78 patients who achieved cCR upon initial assessment and 32 who initially achieved nCR that evolved into cCR upon later reassessment (Figure 2A). One patient who achieved an initial cCR opted for TME. Patients treated with induction LCCRT followed by consolidation chemotherapy had higher rates of WW eligibility than those treated with induction chemotherapy followed by consolidative LCCRT (50% for induction LCCRT versus 43% for consolidation LCCRT; Figure 2B).

Of the 109 WW patients, 88 (81%) patients had a sustained cCR and 21 (19%) patients experienced local regrowth (20 endoluminal regrowths and 1 extraluminal nodal regrowth) (Figure 2A and Supplementary Table S3, available at https://doi.org/10.1016/j.annonc.2024.07.729). Of the 88 patients with sustained cCR, 64 (73%) occurred in patients who achieved cCR on initial assessment and 24

Table 1. Demographics and clinical characteristics by cohort. AV, anal verge; BMI, body mass index; ECOG, Eastern Cooperative Oncology Group; IHC, immunohistochemistry; IQR, interquartile range; LCCRT, long-course chemoradiotherapy; MMR, mismatch repair; NA, not applicable; SCRT, short-course radiotherapy; TME, total mesorectal excision.

Characteristic	Overall (n = 323)	LCCRT (n = 247)	SCRT (n = 76)	P value
Age, median (IQR), years	56.0 (49.0-67.0)	57.0 (49.0-67.0)	55.5 (49.0-66.0)	0.929
Sex, *n* (%)				0.987
Male	200 (61.9)	153 (61.9)	47 (61.8)	
Female	123 (38.0)	94 (38.1)	29 (38.2)	
Race and ethnicity, *n* (%)				0.207
Asian/Pacific Islander	27 (8)	17 (7)	10 (13)	
Hispanic	30 (9)	26 (11)	4 (5)	
Non-Hispanic black	13 (4)	9 (4)	4 (5)	
Non-Hispanic caucasian	244 (76)	189 (77)	55 (73)	
Other/unknown	9 (3)	6 (2)	3 (4)	
BMI, median (IQR), kg/m^2	27.1 (24.2-31.7)	27.2 (24.6-32.0)	26.4 (23.5-31.0)	0.168
Unknown	15	15	0	
ECOG scale, *n* (%)				>0.999
0, 1	301 (99.7)	225 (99.6)	76 (100.0)	
≥2	1 (0.3)	1 (0.4)	0 (0.0)	
Unknown	21	21	0	
Clinical stage, *n* (%)				0.996
cStage I	10 (3.1)	9 (3.7)	1 (1.3)	
cStage II	44 (13.7)	32 (13.0)	12 (15.8)	
cStage III	268 (83.2)	205 (83.3)	63 (82.9)	
Unknown	1	1	0	
cT stage, *n* (%)				0.411
cT1	5 (1.5)	3 (1.2)	2 (2.6)	
cT2	27 (8.3)	17 (6.9)	10 (13.2)	
cT3	230 (71.4)	181 (73.6)	49 (64.5)	
cT4	60 (18.6)	45 (18.3)	15 (19.7)	
Unknown	1	1	0	
cN stage, *n* (%)				0.940
cN negative	56 (17.4)	43 (17.5)	13 (17.1)	
cN positive	266 (82.6)	203 (82.5)	63 (82.9)	
Unknown	1	1	0	
Tumor location, *n* (%)				0.284
AV <5 cm	119 (37.4)	95 (39.3)	24 (31.6)	
5 ≤ AV < 10 cm	156 (49.1)	115 (47.5)	41 (53.9)	
AV ≥10 cm	43 (13.5)	32 (13.2)	11 (14.5)	
Unknown	5	5	0	
Tumor size, median (IQR), cm	4.3 (3.4-5.6)	4.4 (3.4-5.6)	4.3 (3.4-5.4)	0.410
Unknown	9	9	0	
Histologic grade, *n* (%)				0.355
Low grade	298 (92.3)	226 (91.5)	72 (94.7)	
High grade	25 (7.7)	21 (8.5)	4 (5.3)	
Loss of MMR ≥1 in IHC, *n* (%)	8 (2.7)	8 (3.7)	0 (0.0)	0.205
Unknown	36	29	7	
Extra TME Node, *n* (%)	87 (27.7)	60 (25.1)	27 (36.0)	0.066
Unknown	9	8	1	
Mesorectal fascia involve (≤1 mm), *n* (%)	133 (47.8)	99 (47.6)	34 (48.6)	0.888
Unknown	45	39	6	
Extramural depth of invasion, median (IQR), mm	4.0 (3.0-7.0)	4.0 (3.0-7.0)	4.0 (2.0-6.0)	0.080
Unknown	53	42	11	
Extramural venous invasion, *n* (%)	NA	NA	NA	0.129
Absent	237 (77.2)	180 (77.6)	57 (76.0)	
Equivocal	22 (7.2)	13 (5.6)	9 (12.0)	
Present	48 (15.6)	39 (16.8)	9 (12.0)	
Unknown	16	15	1	

(27%) occurred in patients who initially achieved nCR that evolved into cCR upon later assessment. Of the 21 local regrowth cases, 13 (62%) occurred in patients who achieved cCR on initial assessment and 8 (38%) occurred in those who evolved from nCR to cCR.

Distant metastases occurred in 16 (15%) of the 109 WW patients, comprising 8 patients who achieved cCR on initial assessment and 8 patients who achieved nCR that evolved into cCR (Supplementary Table S3, available at https://doi.org/10.1016/j.annonc.2024.07.729). Of the 88 patients with a sustained cCR, 10 patients (11%) developed distant metastases (7 lung, 2 liver, and 1 peritoneal). Of the 21 patients who experienced local regrowth, 6 (29%) developed distant metastases (4 liver, 1 lung, and 1 diffuse) (Supplementary Table S4 and Figure S4, available at https://doi.org/10.1016/j.annonc.2024.07.729).

Table 2. Treatment characteristics by cohort. 3DCRT, three-dimensional conformal radiotherapy; 5-FU, 5-fluorouracil; cCR, clinical complete response; cGy, centi-Gray; IMRT, intensity-modulated radiation therapy; IQR, interquartile range; LCCRT, long-course chemoradiotherapy; nCR, near complete response; SCRT, short-course radiotherapy; SD, standard deviation; TNT, total neoadjuvant treatment.

Characteristic	Overall ($N = 323$)	LCCRT ($N = 247$)	SCRT ($N = 76$)	*P* value
Type of TNT, *N* (%)				0.178
Induction chemotherapy + consolidation chemoradiation	244 (75.5)	191 (77.3)	53 (69.7)	
Induction chemoradiation + consolidation chemotherapy	79 (24.5)	56 (22.7)	23 (30.3)	
Radiation dose received, median (IQR), cGy	5040 (4500-5400)	5400 (5010-5400)	2500 (2500-2500)	<0.001
Radiation duration, median (IQR), days	33 (33-40)	38 (37-41)	5 (5-7)	<0.001
Radiation modality, *n* (%)				0.093
3DCRT	115 (35.9)	95 (38.9)	20 (26.3)	
IMRT	204 (63.8)	148 (60.7)	56 (73.7)	
Proton	1 (0.3)	1 (0.4)	0 (0)	
Unknown	3	3	0	
Day of chemoradiation initiation, *n* (%)				0.022
Monday	158 (49.2)	112 (45.7)	46 (60.5)	
Tuesday	55 (17.1)	50 (20.4)	5 (6.6)	
Wednesday	58 (18.1)	45 (18.4)	13 (17.1)	
Thursday	40 (12.5)	30 (12.2)	10 (13.2)	
Friday	10 (3.1)	8 (3.2)	2 (2.6)	
Unknown	2	2	0	
Regimen of chemoradiation, *n* (%)				<0.001
None (radiation only)	78 (23.5)	2 (0.8)	76 (100.0)	
Capecitabine	239 (74.0)	239 (96.8)	0 (0.0)	
5-FU	5 (1.5)	5 (2.0)	0 (0.0)	
FOLFOX	1 (0.3)	1 (0.4)	0 (0.0)	
Regimen of chemotherapy, *n* (%)				0.816
Oxaliplatin-based (FOLFOX or CAPOX)	313 (96.9)	238 (96.4)	75 (98.7)	
Single-agent (5-FU or capecitabine)	8 (2.4)	7 (2.8)	1 (1.3)	
Irinotecan-based (FOLFIRI or FOLFIRINOX)	2 (0.6)	2 (0.8)	0 (0.0)	
Interval from chemotherapy to chemoradiation, median (IQR), weeks	3.9 (2.9-5.0)	3.9 (2.7-5.0)	4.4 (3.4-5.7)	0.064
Interval from chemoradiation to chemotherapy, median (IQR), weeks	4.7 (3.4-8.6)	5.4 (3.5-9.1)	3.6 (2.4-4.4)	0.004
Duration of chemotherapy, median (IQR), weeks	14.0 (12.3-15.0)	14.0 (13.7-15.0)	14.0 (10.8-15.0)	0.072
Unknown	8	8	0	
Duration of TNT, median (IQR), weeks	22.6 (20.5-24.8)	23.5 (21.9-25.2)	18.8 (16.0-20.3)	<0.001
Unknown	5	5	0	
Interval to restaging, median (IQR), weeks	8.3 (6.1-10.4)	8.0 (6.0-10.3)	9.0 (7.3-10.7)	0.111
Unknown	7	6	1	
Clinical complete response (cCR), *n* (%)				0.863
Yes	143 (44.3)	110 (44.5)	33 (43.4)	
No	177 (54.8)	135 (54.7)	42 (55.2)	
Died before assessment	3 (0.9)	2 (0.8)	1 (1.3)	
Interval to cCR, median (IQR), weeks				
cCR upon initial assessment	8.2 (6.1-10.1)	8.1 (6.6-10.1)	9.1 (7.3-10.6)	0.781
Initial nCR which evolved to cCR	19.7 (16.3-25.4)	20.4 (16.3-25.9)	18.9 (18.0-19.7)	0.235

SCRT-WW cohort

Among the 76 patients treated with SCRT, 33 (43.4%) patients achieved cCR and were eligible for WW management. This included 25 patients who achieved cCR upon initial assessment and 8 patients who initially achieved nCR that evolved into cCR upon later reassessment (Figure 2A). While most patients started SCRT on a Monday and received uninterrupted treatment, there were no observed differences in cCR rate between patients who began SCRT on Monday and those who began SCRT on a non-Monday and had treatment interrupted by the weekend (Supplementary Table S5, available at https://doi.org/10.1016/j.annonc.2024.07.729). Patients treated with induction SCRT followed by consolidation chemotherapy had higher rates of WW eligibility than those initially treated with chemotherapy (52% for induction SCRT versus 40% for consolidation SCRT; Figure 2B).

Of the 33 WW patients, 22 (67%) patients had sustained cCR and 11 (33%) patients experienced local regrowth (10 endoluminal regrowths and 1 extraluminal nodal regrowth). Of the 22 patients with sustained cCR, 18 (82%) occurred in patients who achieved cCR on initial assessment and 4 (18%) occurred in patients who initially achieved nCR that evolved into a cCR (Figure 2A and Supplementary Table S3, available at https://doi.org/10.1016/j.annonc.2024.07.729). Of the 11 local regrowth cases, 7 (64%) occurred in patients who achieved cCR on initial assessment and 4 (36%) occurred in patients who evolved from nCR to cCR.

Distant metastases occurred in 3 (9%) of the 33 WW patients, all of whom achieved cCR on initial assessment (Supplementary Table S3, available at https://doi.org/10.1016/j.annonc.2024.07.729). Of the 22 patients with sustained cCR, 1 (5%) developed distant failure (liver). A total of 2 (18%) of the 11 patients who experienced local

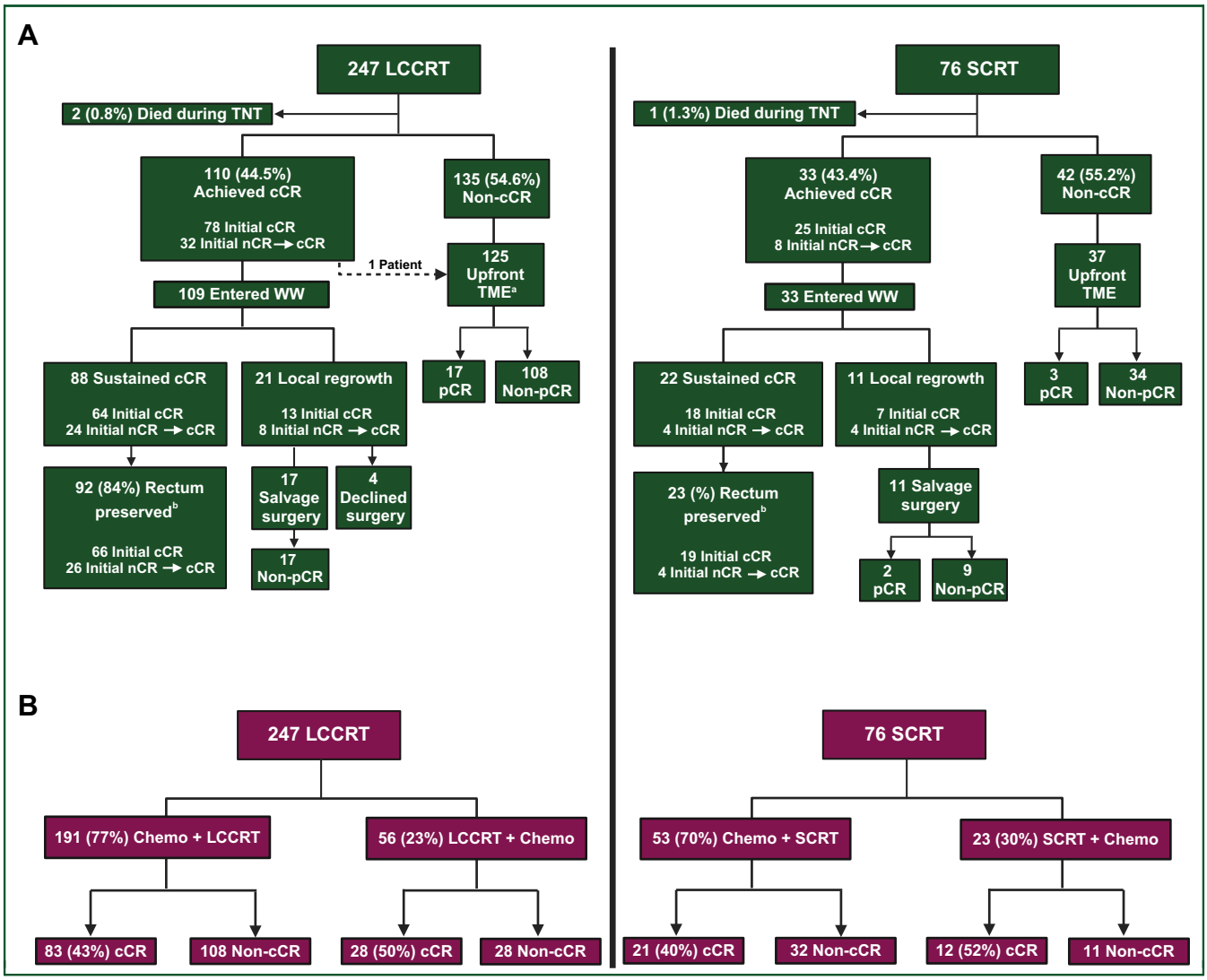

Figure 2. Treatment response categorized by cohort (A) and treatment sequence (B).
cCR, clinical complete response; chemo, chemotherapy; LCCRT, long-course chemoradiotherapy; nCR, near complete response; pCR pathologic complete response; SCRT, short-course radiotherapy; TAE, transanal excision; TME, total mesorectal excision; TNT, total neoadjuvant therapy; WW, watch-and-wait.
[a]Includes one patient with cCR who was offered WW, but declined due to preference for surgery. [b]Includes four patients in LCCRT cohort and one patient in SCRT cohort who underwent TAE for salvage surgery.

regrowth developed distant metastases (liver; liver and lung) (Supplementary Table S6 and Figure S5, available at https://doi.org/10.1016/j.annonc.2024.07.729).

Organ preservation, local regrowth, DFS, and OS among all patients

Among all 323 patients, the 2-year organ preservation rate was 40% (95% CI 34% to 46%) for the LCCRT cohort and 31% (95% CI 22% to 44%) for the SCRT cohort ($P = 0.4$; Figure 3A). The 2-year distant recurrence (18% LCCRT, 95% CI 13% to 23% versus 21% SCRT, 95% CI 10% to 30%; $P = 0.6$; Figure 3B), DFS (79% LCCRT, 95% CI 74% to 85% versus 70% SCRT, 95% CI 61% to 82%; $P = 0.07$; Figure 3C), and OS (96% LCCRT, 95% CI 93% to 98% versus 92% SCRT, 95% CI 86% to 98%; $P = 0.2$; Figure 3D) rates were similar between LCCRT and SCRT cohorts.

Organ preservation, local regrowth, DFS, and OS among WW patients

Among the 142 (109 LCCRT, 33 SCRT) patients who entered WW management, LCCRT-based TNT resulted in statistically higher 2-year organ preservation (89% LCCRT, 95% CI 83% to 95% versus 70% SCRT, 95% CI 55% to 90%; $P = 0.005$; Figure 4A) and lower 2-year local regrowth (19% LCCRT, 95% CI 11% to 26% versus 36% SCRT, 95% CI 16% to 52%; $P = 0.07$; Figure 4B) compared with SCRT-based TNT. The 2-year distant recurrence (10% LCCRT, 95% CI 4% to 16% versus 6% SCRT, 95% CI 0% to 14%; $P = 0.5$; Supplementary Figure S6, available at https://doi.org/10.1016/j.annonc.2024.07.729), DFS (90% LCCRT, 95% CI 84% to 96% versus 90% SCRT, 95% CI 80% to 100%; $P = 0.8$; Figure 4C), and OS (99% LCCRT, 95% CI 97% to 100% versus 100% SCRT, 95% CI 100% to 100%; $P = 0.4$; Figure 4D) were similar between LCCRT and SCRT patients managed by WW.

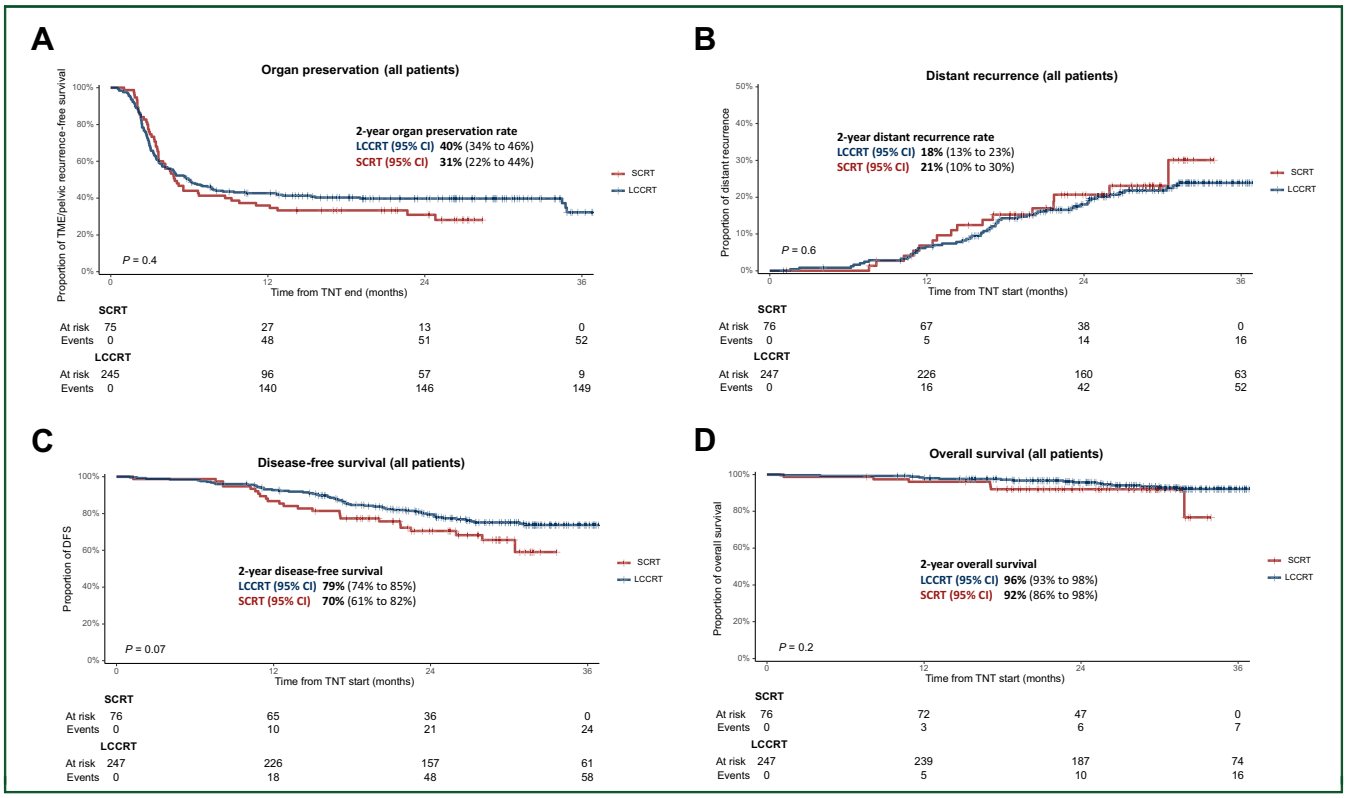

Figure 3. Organ preservation (A), local regrowth (B), disease-free survival (C), and overall survival (D) curves for all patients.
CI, confidence interval; DFS, disease-free survival; LCCRT, long-course chemoradiotherapy; SCRT, short-course radiotherapy; TME, total mesorectal excision; TNT, total neoadjuvant therapy.

Surgical salvage after local regrowth among WW patients

A total of 17 of the 21 LCCRT-based TNT patients with local regrowth were successfully salvaged with surgery (13 TME and 4 TAE), whereas the remaining 4 patients declined surgery (Figure 2 and Supplementary Table S3, available at https://doi.org/10.1016/j.annonc.2024.07.729**)**. All 11 SCRT-based TNT patients with local regrowth were successfully salvaged with surgery (10 TME and 1 TAE) (Figure 2 and Supplementary Table S3, available at https://doi.org/10.1016/j.annonc.2024.07.729). There were no differences in permanent stoma rates, operative time, blood loss, or morbidity between salvage cases following LCCRT and SCRT (Supplementary Table S7, available at https://doi.org/10.1016/j.annonc.2024.07.729). Among the patients who underwent salvage TME, one (6%) in the LCCRT group and one (9%) in the SCRT group developed pelvic recurrence. No recurrences were observed after salvage TAE. Distant failure occurred in one LCCRT patient and one SCRT patient following salvage surgery.

Patient-reported quality of life among WW patients

Self-reported LARS-Q results were obtained from WW patients at baseline ($n = 55$), as well as at 6 months ($n = 28$) and 12 months ($n = 47$) following TNT completion. The percentage of WW patients reporting major LARS symptoms following TNT were similar: 21% ($n = 7$) for LCCRT versus 18% ($n = 4$) for SCRT at baseline; 38% ($n = 6$) for LCCRT versus 42% ($n = 5$) for SCRT at 6 months, and 22% ($n = 6$) for LCCRT versus 15% ($n = 3$) for SCRT at 12 months (Supplementary Table S8, available at https://doi.org/10.1016/j.annonc.2024.07.729).

Local recurrence, distant recurrence, and DFS and OS among patients who underwent upfront surgery

One hundred and sixty-two patients underwent upfront surgery including 125 (51%) in the LCCRT cohort and 37 (49%) in the SCRT cohort (Figure 2). There was no difference in the interval between the date of TNT completion to the date of upfront surgery [median (IQR), 12.7 weeks (10.1-18.9 weeks) for LCCRT versus 15.4 weeks (11.9-20.0 weeks) for SCRT]. Among patients who underwent upfront surgery, there were no differences in surgical procedure, operative time, estimated blood loss, morbidity, or permanent stoma rates (Supplementary Table S9, available at https://doi.org/10.1016/j.annonc.2024.07.729) between cohorts. The R0 resection rates (98% for LCCRT and 100% for SCRT; $P > 0.9$) and pathologic complete response (pCR) rates (14% for LCCRT and 8% for SCRT; $P = 0.6$) were similar. While there was no difference in 2-year local recurrence (5.1% LCCRT, 95% CI 1.0% to 9.0% versus 2.8% SCRT, 95% CI 0% to 8.0%; $P > 0.9$; Supplementary Figure S7A, available at https://doi.org/10.1016/j.annonc.2024.07.729), distant recurrence (22% LCCRT, 95% CI 15% to 29% versus 34% SCRT, 95% CI 15% to 48%; $P = 0.2$; Supplementary Figure S7B, available at https://doi.org/10.1016/j.annonc.2024.07.729), or OS (96% LCCRT, 95% CI 92% to 99% versus 92% SCRT, 95% CI

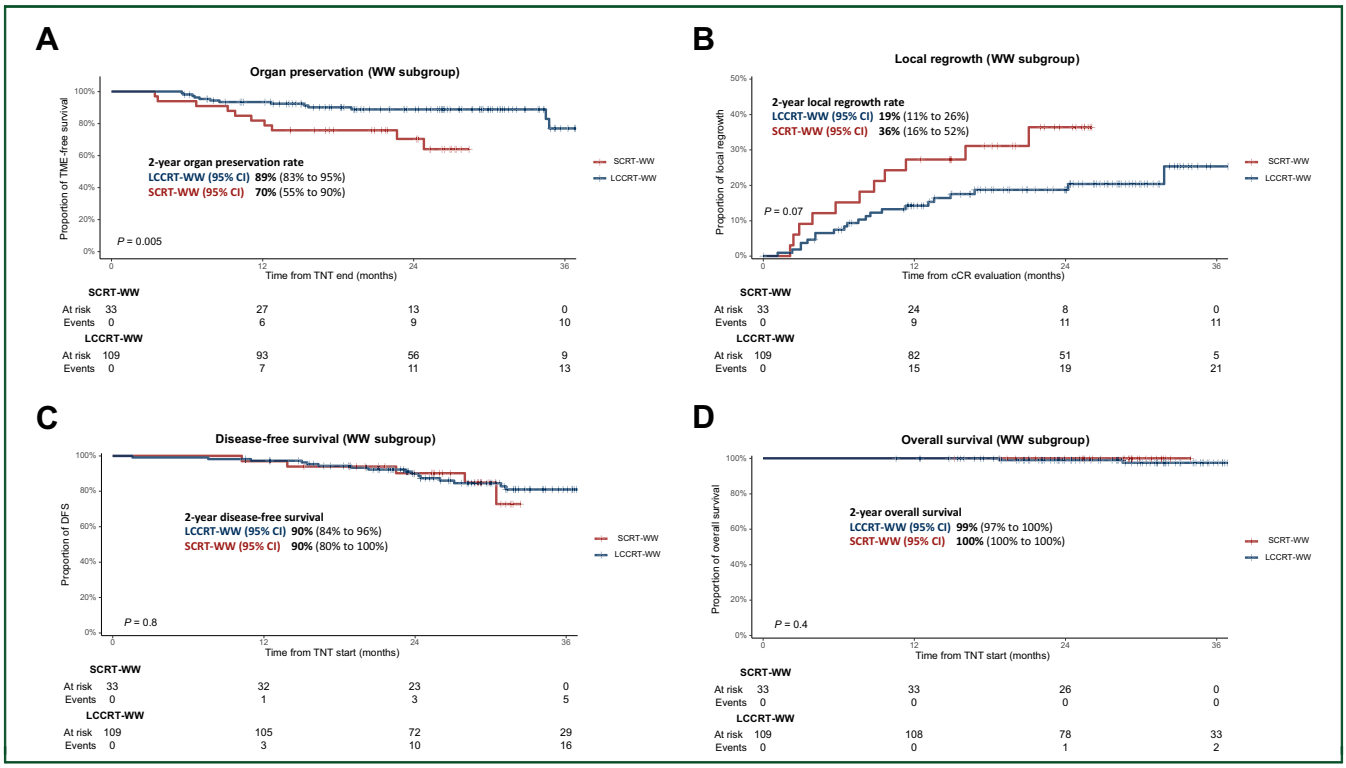

Figure 4. Organ preservation (A), local regrowth (B), disease-free survival (C), and overall survival (D) curves for WW patients.
cCR, clinical complete response; CI, confidence interval; DFS, disease-free survival; LCCRT, long-course chemoradiotherapy; SCRT, short-course radiotherapy; TME, total mesorectal excision; TNT, total neoadjuvant therapy; WW, watch-and-wait.

84% to 100%; $P = 0.6$; Supplementary Figure S7C, available at https://doi.org/10.1016/j.annonc.2024.07.729), patients treated with SCRT-based TNT followed by upfront surgery had worse 2-year DFS (75% LCCRT, 95% CI 68% to 83% versus 57% SCRT, 95% CI 43% to 77%; $P = 0.03$; Supplementary Figure S7D, available at https://doi.org/10.1016/j.annonc.2024.07.729).

DISCUSSION

This study is the first to compare the oncologic efficacy of organ preservation following LCCRT- and SCRT-based TNT regimens. Our findings indicate that similar WW eligibility rates are achieved with LCCRT and SCRT (44.5% versus 43.4%). We observed higher organ preservation and lower local regrowth rates, however, in WW patients treated with LCCRT compared with SCRT. Importantly, there were no differences in distant failure, DFS, or OS rates between the WW cohorts. There were also no differences in local regrowth and distant failure rates between patients who achieved cCR immediately post-TNT and those who initially achieved nCR that evolved to cCR. In both LCCRT- and SCRT-based TNT cohorts, higher organ preservation rates were observed with induction radiotherapy followed by consolidation chemotherapy than those treated initially with chemotherapy. To our knowledge, we are the first to report demonstrating the oncological efficacy of consolidation SCRT in a TNT regimen. Together these data support induction LCCRT followed by consolidation chemotherapy as the preferred TNT regimen for patients with locally advanced rectal cancer pursuing organ preservation.

While some retrospective series have shown an association between local regrowth and distant metastases in WW patients,[25,36-38] we observed no difference in oncological outcomes and survival between LCCRT and SCRT cohorts, despite observing a higher local regrowth rate in WW patients treated with SCRT (Figure 4 and Supplementary Figure S6, available at https://doi.org/10.1016/j.annonc.2024.07.729). While LCCRT patients who underwent surgical salvage had similar 2-year DFS as those who underwent upfront surgery (88% salvage versus 75% upfront), SCRT patients who underwent surgical salvage had higher DFS than those who underwent upfront surgery (72% salvage versus 57% upfront; Supplementary Figure S8, available at https://doi.org/10.1016/j.annonc.2024.07.729). These findings suggest that delaying surgery in favor of organ preservation does not jeopardize oncological outcomes or increase distant metastatic risk, regardless of radiation dose and fractionation. Thus, patients may undergo salvage surgery without compromising oncologic outcomes, addressing a key concern for clinicians and patients considering WW.

The biological equivalency of LCCRT and SCRT remains under debate, particularly regarding organ preservation. Although SCRT has been shown to be a noninferior alternative to LCCRT in the preoperative setting,[10] emerging evidence suggests that pCR rates are lower and local recurrence rates are higher for patients treated with

SCRT-based TNT compared with LCCRT-based TNT.[39,40] Our observations that WW patients treated with SCRT-based TNT have lower organ preservation rates and higher local regrowth compared with those treated with LCCRT-based TNT will likely add to this skepticism. It remains unclear whether the higher rate of local regrowth following SCRT-based TNT is due to the lower biologically effective dose (BED) of SCRT (Supplementary Table S10, available at https://doi.org/10.1016/j.annonc.2024.07.729) or due to tumor repopulation.[41-45] In this context, counteracting repopulation by accelerating treatment may be more effective to control microscopic disease when surgery is planned than gross disease when surgery is not planned. The ongoing German Rectal Cancer Study Group ACO/ARO/AIO-18.1 trial (NCT04246684) will provide prospective data on the durability of cCR relative to SCRT and LCCRT to help answer some of these questions. Differences in treatment protocols (e.g. radiation dose, addition of oxaliplatin to concurrent chemotherapy regimen, and duration of consolidation chemotherapy regimens) will complicate direct comparison to our study. ACO/ARO/AIO-18.1, however, should provide a definitive conclusion regarding WW outcomes for LCCRT-based and SCRT-based TNT. Additionally, the planned pooled analysis of ACO/ARO/AIO-18.1, JANUS, and the Japanese EMSEMBLE trials will allow us to evaluate the relative contribution of BED and tumor repopulation kinetics to organ preservation in the context of TNT.[46]

Our observational study assessed outcomes and impacts of a pandemic-driven policy change, rendering it a natural experiment.[47-51] The COVID-19 mandates minimized selection bias, thereby creating a consecutive cohort of patients treated uniformly with SCRT-based TNT during mandate periods for comparison with a cohort of patients treated with LCCRT-based TNT during peri-mandate periods. The impact of COVID on survival in the SCRT cohort represents an important potential source of bias. Reassuringly, OS was similar between cohorts and no patients died directly due to COVID, suggesting that our mandates were effective in ensuring patient protection. We observed a higher proportion of *SMAD4* genetic alterations in our SCRT cohort, which will require additional investigation given *SMAD4* alterations have been associated with aggressive clinicopathologic characteristics and carry a poor prognosis in colorectal cancer.[52,53] To minimize immortal time bias, organ preservation time was calculated from the date of TNT completion, whereas most of the time-dependent analyses were evaluated from the date of TNT initiation. Although median follow-up in this study was 30.4 months, the phase II OPRA trial demonstrated that the majority (∼95%) of local regrowth events occur within the first 24 months after TNT completion,[4] a finding that has been reinforced by several other series.[15,25,54] Despite the longer follow-up in the LCCRT cohort, the local regrowth rate was reassuringly lower than in the SCRT cohort. Moreover, given the aforementioned concerns for increased locoregional failure following SCRT-based TNT,[40] long-term reassessment of our series will be important. Finally, while we did not observe differences in bowel function between LCCRT and SCRT in patients on WW management, these results should be interpreted with caution given the modest response rates and limited assessment timepoints.

This natural experiment demonstrates that TNT regimens integrating LCCRT and SCRT can achieve similar WW eligibility; however, WW patients treated with SCRT had higher local regrowth and lower organ preservation rates than those treated with LCCRT. These findings provide timely insights for patients considering organ preservation strategies and support induction LCCRT followed by consolidation chemotherapy as the preferred TNT regimen for patients with locally advanced rectal cancer seeking an optimal tumor response and organ preservation.

ACKNOWLEDGEMENTS

The authors acknowledge the entire Colorectal Disease Management Team at Memorial Sloan Kettering Cancer who provided exceptional care to these patients. The authors also thank Jennifer Huber, PhD, for editorial support. Certain figures (Visual Abstract and Figure 2) were created with the assistance of BioRender.com.

FUNDING

This work was supported in part by a National Institutes of Health/National Cancer Institute, NIH/NCI) Memorial Sloan Kettering Cancer Center (MSK) support grant [grant number P30 CA008748]; an NIH/NCI grant [grant number R37 CA248289 to JJS]; an NIH/NCI grant [grant number K08 CA255574 to PBR]; an NCI Surgical Oncology T32 research training grant [grant number 5T32 CA 9501-34 to AB].

DISCLOSURE

PBR received research funding (2019) and serves as a consultant for EMD Serono (2018-present), receives research funding from XRAD Therapeutics (2022-present), is a consultant for Faeth Therapeutics (2022-present), is a consultant for Natera (2022-present), and is a volunteer on the advisory board for the HPV Cancers Alliance and Anal Cancer Foundation non-profit organizations. JJS received travel support for fellow education from Intuitive Surgical (August 2015). He also served as a clinical advisor for Guardant Health (March 2019) and as a clinical advisor for Foundation Medicine (April 2022). He served as a consultant and speaker for Johnson and Johnson (May 2022), and he serves as a clinical advisor and consultant for GlaxoSmithKline (2023-2024). JGA owns stock in Intuitive Surgical and receives as Honoraria for Johnson & Johnson and Intuitive Surgical. He is also a consultant for Medtronic, Intuitive Surgical, and Johnson & Johnson. MRW serves as a consultant for Precisca and as a section editor for UpToDate. AC receives research funding from Seagen, Rgenix, and GlaxoSmithKline. She also serves as a consultant for Bayer, GlaxoSmithKline, Incyte, Merck, Janssen, Seagen, and G1 Therapeutics. LBS serves as a consultant for Genor BioPharma. JS serves as a consultant for PAIGE.AI. MJG serves as a consultant for GlaxoSmithKline. NH receives honoraria

from Bayer and serves as a consultant for Guerbet. CHC received honoraria from Elekta, owns stock in Oncturnal, and serves as a consultant for TriSalus. LD is a consultant for Merck, NeoPhore, and Personal Genome Diagnostics. NHS received research funding from Roche/Genentech, Pfizer, Merck, BMS, AstraZeneca, Puretech, Immunocore, Regeneron, and Agenus. He serves as a consultant for Agenus, ABL Bio, AstraZeneca, GlaxoSmithKline, Novartis, Numab, Puretech, and Regeneron. All other authors have declared no conflicts of interest.

DATA SHARING

The datasets generated and analyzed during the current study will be available on reasonable request and pursuant to Memorial Sloan Kettering Cancer Center guidelines. Please contact the corresponding author (P. B. Romesser) to request the data from this study.

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