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Nonoperative Rectal Cancer Management With Short-Course Radiation Followed by Chemotherapy: A Nonrandomized Control Trial

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Abstract

Short-course radiation therapy results in higher pathologic complete response than long-course chemoradiation therapy in rectal adenocarcinoma. All definitive treatment experiences with nonoperative intent have used long-course chemoradiation. This prospective clinical trial of 20 patients is the first experience of nonoperative management with short-course radiation followed by chemotherapy. We observed a high clinical complete response rate with no severe late toxicity.

Purpose: Short-course radiation therapy (SCRT) and nonoperative management are emerging paradigms for rectal cancer treatment. This clinical trial is the first to evaluate SCRT followed by chemotherapy as a nonoperative treatment modality. **Methods:** Patients with nonmetastatic rectal adenocarcinoma were treated on the single-arm, Nonoperative Radiation Management of Adenocarcinoma of the Lower Rectum study of SCRT followed by chemotherapy. Patients received 25 Gy in 5 fractions to the pelvis followed by FOLFOX ×8 or CAPOX ×5 cycles. Patients with clinical complete response (cCR) underwent nonoperative surveillance. The primary end point was cCR at 1 year. Secondary end points included safety profile and anorectal function. **Results:** From June 2016 to March 2019, 19 patients were treated (21% stage I, 32% stage II, and 47% stage III disease). At a median follow-up of 27.7 months for living patients, the 1-year cCR rate was 68%. Eighteen of 19 patients are alive without evidence of disease. Patients with cCR versus without had improved 2-year disease-free survival (93% vs 67%; $P = .006$), distant metastasis-free survival (100% vs 67%; $P = .03$), and overall survival (100% vs 67%; $P = .03$). Involved versus uninvolved circumferential resection margin on magnetic resonance imaging was associated with less initial cCR (40% vs 93%; $P = .04$). Anorectal function by Functional Assessment of Cancer Therapy-Colorectal cancer score at 1 year was not different than baseline. There were no severe late effects. **Conclusions:** Treatment with SCRT and chemotherapy resulted in high cCR rate, intact anorectal function, and no severe late effects. NCT02641691.

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Introduction

Colorectal cancer has the third highest incidence and second highest mortality for malignancies worldwide; rectal cancer comprises approximately one-third of colorectal cancers.[1] The majority of patients with stage I to III rectal cancer undergo surgery with potential for impaired rectal function or permanent stoma.[2] The treatment of locally advanced rectal cancer traditionally includes 6 weeks of long-course chemoradiation (LCCRT), chemotherapy, and total mesorectal excision (TME).

Multiple phase III randomized trials have demonstrated that oncologic outcomes after short-course radiation therapy (SCRT) and LCCRT are similar when combined with TME.[3–6] Institutional studies indicate that rectal cancer can be managed nonoper-

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atively after a clinical complete response (cCR) to LCCRT[7–10] and that neoadjuvant chemotherapy increases the pathologic complete response rate.[11] Recently, the Rectal Cancer and Pre-operative Induction Therapy Followed by Dedicated Operation (RAPIDO) study demonstrated that, compared with LCCRT, SCRT followed by chemotherapy (SCRT-CH) has a higher pathologic complete response rate, less disease-related treatment failure, and superior distant metastasis-free survival (DMFS).[12] No differences were found in overall health, quality of life and low anterior resection (LAR) syndrome score.[12] Thus, SCRT with nonoperative intent may become an increasingly used treatment paradigm. Here we report the first prospective data on SCRT-CH for nonoperative management of nonmetastatic rectal adenocarcinoma.

Methods

Nonoperative Radiation Management of Adenocarcinoma of the Lower Rectum (NORMAL-R) is a prospective, nonrandomized trial designed and conducted by the lower GI focus group at Washington University School of Medicine. The trial was approved by our Institutional Review Board and registered in Clinicaltrials.gov (NCT02641691). Informed consent was obtained for all patients.

Patients 18 years or older, with an Eastern Collaborative Oncology Group performance status of 0 to 2 and biopsy-proven stage I to IIIB invasive rectal adenocarcinoma were eligible. Participants were staged with colonoscopy, pelvic magnetic resonance imaging, and a computed tomography scan of the chest and abdomen. Distal tumor edge needed to be within 12 cm of the anal verge. Exclusion criteria included clinical T4 disease, clinically undetectable disease, prior treatment for rectal cancer, prior pelvic radiation, allergies to trial chemotherapeutics, and uncontrolled intercurrent illness.

Patients were treated with 25 Gy in 5 daily fractions of pelvic radiation, with a daily cone beam computed tomography scan, delivered over a single calendar week. Simultaneous integrated boosts of 30 Gy to primary and 35 Gy to extramesorectal lymph nodes were permitted. Clinical target volume 25 Gy included the rectum and mesorectal compartment and planning target volume was a symmetrical margin of 0.7 cm. Dose constraints were small bowel maximum dose of less than 25 Gy and 95% prescription covers 100% of the planning target volume.

Multiagent chemotherapy was started when acute radiation symptoms improved, between 2 and 4 weeks after SCRT. Patients were prescribed FOLFOX every 2 weeks or CAPOX every 3 weeks. FOLFOX consisted of a fluorouracil bolus (400 mg/m^2, day 1), fluorouracil continuous infusion (2400 mg/m^2, 46 hours starting day 1), leucovorin (400 mg/m^2, day 1), and oxaliplatin (85 mg/m^2, day 1). CAPOX consisted of oxaliplatin (130 mg/m^2, day 1) and capecitabine (1000 mg/m^2 twice daily, days 1-14). When the trial initially opened, patients were treated with 4 cycles of FOLFOX. The protocol was later amended to prescribe 8 cycles of FOLFOX or 5 cycles of CAPOX.

Patients were assessed for clinical response 3 to 8 weeks after chemotherapy completion with pelvic magnetic resonance imaging, endoscopy (sigmoidoscopy preferred, proctoscopy accepted), and digital rectal examination. cCR was defined as (1) no ulceration, nodularity or visible tumor on endoscopy, (2) no intermediate to bright T2 signal or suspicious lymph nodes (based on size, border irregularity, signal heterogeneity and round shape[17]) on magnetic resonance imaging, and (3) no induration or palpable tumor present on digital rectal examination.[7,9,10,13] Equivocal endoscopic findings were biopsied. All patient imaging and endoscopic findings were discussed in multidisciplinary tumor review and consensus reached before recommending nonoperative management to the patient. A clinical partial response (cPR) was defined as any response less than cCR. Patients with cCR underwent nonoperative management with magnetic resonance imaging, endoscopy, and digital rectal examination every 3 months. Those with cPR underwent further chemotherapy or TME at the discretion of the treating physician.

The primary end point was the proportion of patients undergoing nonoperative management with persistent cCR at 1 year after RT. Prespecified secondary end points included 1-year post-RT anorectal function per the Functional Assessment of Cancer Therapy-Colorectal Cancer (FACT-C) and severe adverse events per Common Terminology Criteria for Adverse Events Version 4.0 during treatment and at 1 year after radiation. The FACT-C questionnaires were collected before radiation therapy, at the completion of chemotherapy, and at 1 year (10-14 months) after radiation.

This prospective pilot trial was designed to demonstrate proof of concept for nonoperative management with SCRT-CH. Previous studies report a cCR rate 40% with LCCRT.[14] A sample size of 20 patients was required to detect a difference between 40% and 70% in cCR with 80% power at the 0.05 level of significance as determined by a 2-sided exact test. An interim analysis was specified with early termination if fewer than 3 of 10 patients at completion of chemotherapy remained eligible nonoperative candidates. The FACT-C scores at different time points were compared using a linear mixed effects model to account for missing data. Pairwise comparison of the estimated marginal mean quality of life values with Bonferroni correction for multiple comparisons.

Nonprespecified post hoc survival analyses included local regrowth-free survival, TME-free survival, regional control, DMFS, overall survival (OS), and disease-free survival (DFS). Local regrowth-free survival, regional control, DMFS, and OS were calculated from the end of RT to the date of local regrowth, regional recurrence, distant recurrence, and death from any cause, respectively. DFS events included the earliest of regional or distant recurrence or death from any cause. DFS events also included local regrowth in the initial cPR group, but excluded local regrowth in the initial cCR group if the local regrowth was successfully salvaged. TME-free survival was calculated from the completion of RT to TME. Patients who did not develop events were censored at last follow-up. Additional post hoc analyses included log-rank comparisons of the survival end points between patients with an initial cCR versus initial cPR. A P value of less than .05 was considered statistically significant and all P values were 2-sided. All analyses were performed in R, version 4.0.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results

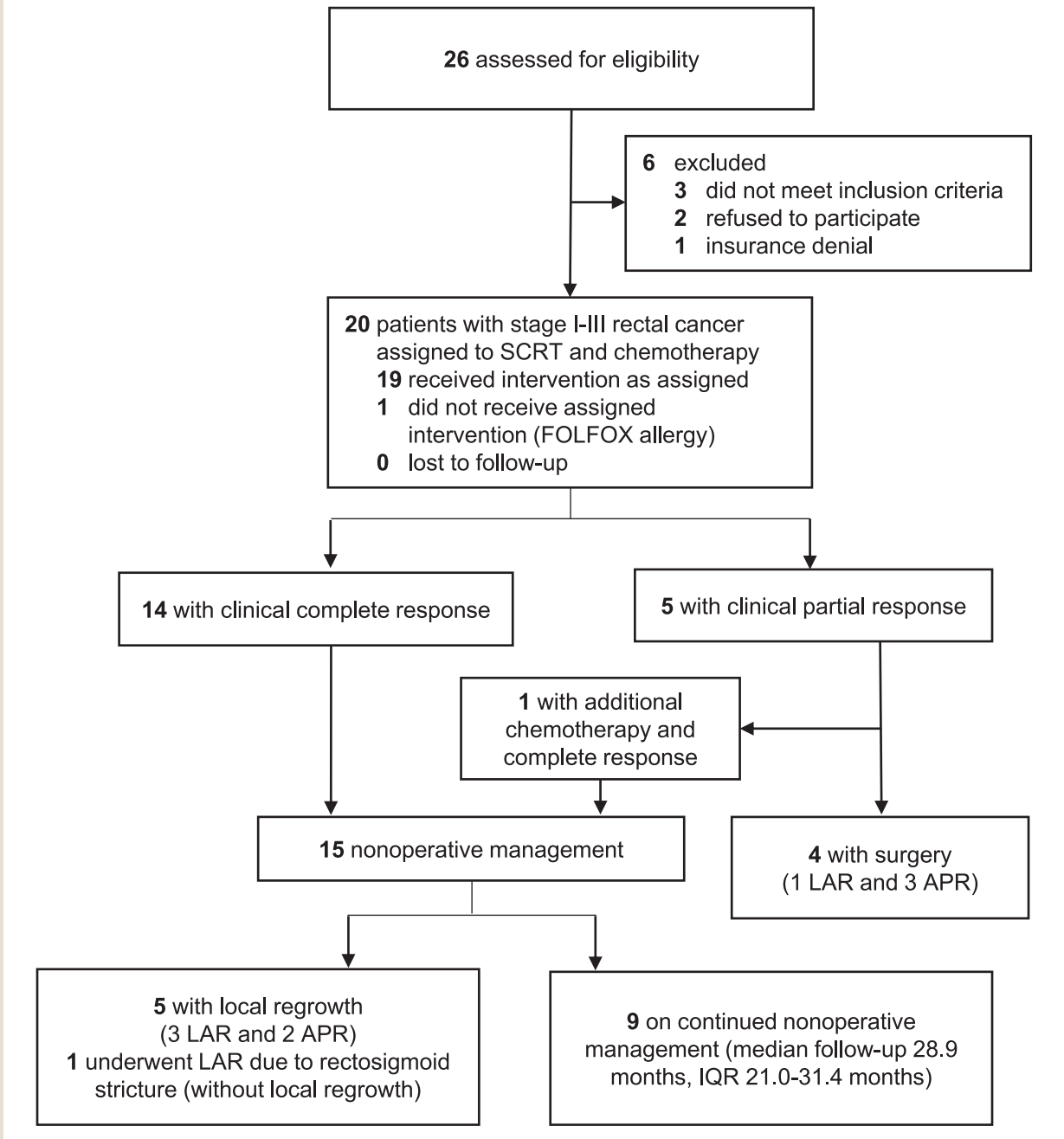
Between June 2016 and March 2019, 20 patients were enrolled (Table 1). Patient accrual was initially limited owing to competing enrollment prioritization on Organ Preservation in Rectal Adeno-

Table 1 Baseline Patient, Tumor, and Treatment Characteristics of All Patients and Comparison Between Patients With an cCR Versus cPR After SCRT and Chemotherapy

Characteristics	All ($N = 19$), Patients (%) or Median (IQR)	cCR ($n = 15$), Patients (%) or Median (IQR)	cPR ($n = 4$), Patients (%) or Median (IQR)	*P* Value
Age	56 (50-63)	54 (48-63)	61 (58-63)	.4
Sex				.1
Female	8 (42)	8 (53)	0 (0)	
Male	11 (58)	7 (47)	4 (100)	
Ethnicity				>.99
White	18 (95)	14 (93)	4 (100)	
Black	1 (5)	1 (7)	0 (0)	
ECOG				.3
0	14 (74)	12 (80)	2 (50)	
1	5 (26)	3 (20)	2 (50)	
T Stage				.5
2	5 (26)	5 (33)	0 (0)	
3	14 (74)	10 (67)	4 (100)	
N Stage				.8
0	10 (53)	7 (47)	3 (75)	
1	7 (37)	6 (40)	1 (25)	
2	2 (11)	2 (13)	0 (0)	
Group stage				.1
I	4 (21)	4 (27)	0 (0)	
II	6 (32)	3 (20)	3 (75)	
III	9 (47)	8 (53)	1 (25)	
Locally advanced	15 (79)	11 (73)	4 (100)	.5
Primary tumor size (cm)	4.0 (3.0-5.8)	3.7 (3.0-4.3)	6.2 (5.4-6.8)	.05
Distance from anal verge (cm)	4.0 (2.0-5.5)	4.0 (2.0-6.5)	3.5 (2.5-4.2)	.5
mrCRM involvement	5 (26)	2 (13)	3 (75)	.04
RT duration (days)	5.0 (5.0-5.1)	5.0 (5.0-5.0)	5.1 (5.0-5.9)	.3
RT primary tumor boost	5 (26)	4 (27)	1 (25)	>.99
RT nodal boosts	4 (21)	3 (20)	1 (25)	>.99
RT any boost(s)	7 (37)	5 (33)	2 (50)	.6
Neoadjuvant CHT agents				>.99
CAPOX	1 (5)	1 (7)	0 (0)	
(m)FOLFOX	18 (95)	14 (93)	4 (100)	
Neoadjuvant CHT cycles				>.99
4	2 (10)	2 (13)	0 (0)	
6	3 (16)	2 (13)	1 (25)	
8	14 (74)	11 (74)	3 (75)	

Abbreviations: cCR = clinical complete response; CHT = chemotherapy; cPR = clinical partial response; ECOG = Eastern Cooperative Oncology Group; IQR = interquartile range; mrCRM = circumferential resection margin on diagnostic MRI; RT = radiation therapy; SCRT = short-course radiation therapy.
Statistical tests performed: Wilcoxon rank-sum test; Fisher's exact test.

Figure 1 Treatment and follow-up of patients. Chemotherapy entailed FOLFOX (fluorouracil, leucovorin and oxaliplatin) or CAPOX (capecitabine and oxaliplatin). APR = abdominal perineal resection; IQR = interquartile range; LAR = low anterior resection.



carcinoma (OPRA)[13] and RAPIDO.[12] Once the competing trials completed enrollment, this trial accrued 18 of 20 patients in 16 months. One patient received SCRT but had an allergic reaction to chemotherapy and could not complete the prescribed treatment, leaving 19 analyzable patients (Table 1).

All patients successfully completed 5 daily fractions of radiation as prescribed without treatment interruptions. All patients successfully began chemotherapy within 2 to 4 weeks of completing SCRT. The median number of chemotherapy cycles received per protocol was 8 cycles of FOLFOX (range, 4-8 cycles) with 1 patient who received 5 cycles of CAPOX. All patients completed

the chemotherapy prescribed with 5 patients requiring a dose reduction (1 with fluorouracil and oxaliplatin, 1 with capecitabine, and 3 with oxaliplatin). The cumulative dose intensity was 0.70 or more for fluoropyrimidine in all 19 patients and was 0.70 or more for oxaliplatin in 18 patients (95%). The median duration of treatment was 19.6 weeks (range, 12.4-25.3 weeks). Two patients received off-protocol chemotherapy (FOLFIRI ×6 cycles for poor pathologic response and CAPOX ×3 cycles for cPR).

The median time from completion of chemotherapy to first clinical response assessment was 2.0 weeks (interquartile range [IQR], 1.6-2.4 weeks). Fourteen of 19 patients (74%) achieved a cCR at the first assessment after SCRT-CH (Table 2). For the primary end point, 68% of patients (13/19) maintained cCR at 1 year after RT. One patient (Table 2: patient 12) with an initial cPR received 3 cycles of FOLFOX off protocol and then qualified for nonoperative management. Compared with patients with a cCR, patients with a cPR had larger primary tumors (median, 6.2 cm [IQR, 5.4-6.8 cm] vs median, 3.7 cm [3.0-4.3 cm]; $P = .05$) and more circumferential resection margin involvement on diagnostic magnetic resonance imaging (mrCRM) (75% vs 13%; $P = .04$) (Table 1). Involved mrCRM was associated with less initial cCR compared with uninvolved mrCRM (40% [2/5] vs 93% [13/14]; $P = .04$). There was no significant difference between the cCR and cPR groups in the use of boost to the primary tumor (30 Gy/5 fx; $n = 5$) (27% vs 25%; $P > .99$), boost to the lymph nodes (35 Gy/5 fx; $n = 4$) (20% vs 25%; $P > .99$), or any boost(s) ($n = 7$) (33% vs 50%; $P = .6$) (Table 1; Figure 1).

At a median follow-up of 27.7 months (IQR, 21.1-31.4 months) for living patients, 33% of patients (5/15) who underwent nonoperative management developed local tumor regrowth at a median of 13.3 months (IQR, 9.4-16.0 months) after RT completion. The 1-year and 2-year TME-free survival for nonoperative candidates were 87% (95% confidence interval [CI], 71%-100%) and 57% (95% CI, 36%-91%), respectively (Figure 2b). The median TME-free duration for the nonoperative group was 21.6 months (IQR, 16.9-29.2 months). Twelve of the 19 patients were evaluated initially by colorectal surgeons as requiring an APR in the event of incomplete response (Table 2). Four of these 12 APR necessary patients (33%) had not undergone oncologic surgery at most recent follow-up owing to a maintained complete clinical response. All of the patients with local regrowth in the nonoperative group were salvaged successfully, and these patients were all without evidence of disease at last follow-up (Table 2). The treatment regimen did not generally increase salvage surgery difficulty (2 of 5 cases noted increased fibrosis; median estimated blood loss 250 mL [IQR, 88-525 mL]).

The regional control, DMFS, OS, and DFS for all patients are shown in Figure 2c and Figure 2d. No patients developed local tumor regrowth, pelvic recurrences, or metastatic disease during treatment. Regional pelvic recurrences were observed in 13% (2/15) and 50% (2/4) of the patients with cCR and cPR, respectively. The only distant failure and death occurred in a patient who, with an initial cPR, underwent planned APR and developed distant metastatic disease 8 months after surgery, and died from rectal cancer. Compared with patients with cPR, patients with cCR had improved regional control (2 years, 93% [95% CI, 82%-100%] vs 67% [95% CI, 30%-100%]; $P = .006$ by log-rank, Figure 3a), DMFS (2 years, 100% vs 67% [95% CI, 30%-100%]; $P = .03$ by log-rank, Figure 3b), OS (2 years, 100% vs 67% [95% CI, 30%-100%]; $P = .03$ by log-rank, Figure 3c), and DFS (2 years, 93% [95% CI, 82%-100%] vs 67% [95% CI, 30%-100%]; $P = .006$ by log-rank, Figure 3d).

Grade 3 or 4 adverse events during treatment were reported in 10 of 19 patients and grade 4 were reported in 3 patients (all during chemotherapy; Supplemental Table 1). All the effects were reversible with no late grade 3 or 4 effects at last follow-up. One patient with a history of myocardial infarction 4 months before trial enrollment experienced cardiac arrest with successful resuscitation on postoperative day 2 after APR. On most recent follow-up, 8 of 9 patients undergoing nonoperative management reported that their bowel movements were back to prediagnosis baseline without any residual side effects (89% overall).

The FACT-C data were successfully collected for all patients with the exception of at 1 year after radiation for 1 patient (Supplemental Table 2). Compared with the pretreatment baseline, physical well-being was decreased at chemotherapy completion ($P = .04$) and at 1 year after radiation ($P = .01$). Social/family well-being was also decreased at chemotherapy completion ($P = .03$), but were not significantly decreased at the 1-year follow-up ($P = .06$) compared with baseline. Anorectal function per colorectal cancer domain was not different compared with baseline at chemotherapy completion ($P = .07$) or at 1 year after radiation ($P = .12$).

Discussion

To our knowledge, this study is the first reported prospective evaluation of treating nonmetastatic rectal adenocarcinoma patients by SCRT-CH with nonoperative intent. A significant proportion of patients achieved and sustained a cCR without surgery, despite nearly one-half presenting with stage III disease and 15 of the 19 patients (79%) having locally advanced (T3 or node positive) disease. The initial cCR of 74% and 1-year follow-up cCR of 68% are very promising and comparable with those of nonoperative management after LCCRT.[7–9] The median follow-up for living patients is 27.7 months, which exceeds the critical threshold of 24 months in nonoperative studies, by which time the majority of recurrences occur.[8,9,15] Despite the limited size of the study, these data showed statistically significant improved regional control, DFS, DMFS, and OS for patients with cCR versus cPR.

The observation that patients with larger tumors (median 6.2 cm vs 3.7 cm) and mrCRM involvement (75% vs 13%) had more cPR indicates that treatment escalation may be necessary to achieve cCR. It is possible that no effect was found for radiation boost to primary tumor owing to numerically smaller tumors (all ≤5.5 cm) and no tumors with mrCRM among patients that received a boost. These data may serve the backbone of future clinical trials of SCRT-CH and nonoperative management.

All patients with local progression underwent salvage surgery in the form of the operation recommended initially, had nonoperative management not been pursued. One patient developed metastatic disease shortly after surgery and it is not clear if the patient had subclinical metastases or if the delay in surgical resection allowed progression to metastatic disease.[16] On-treatment grade 3 or 4 toxic-

Table 2 Patient Characteristics, Outcomes, and Salvage Therapy

Patient	Initial Clinical Staging	Tumor Size (cm)	Distance from Anal Verge (cm)	Planned Surgery	Clinical Response	Surgery Intent	Surgery Type	Pathologic Response	Pathologic Details	TME-free Duration (mo)	cCR at 1 Year	Recurrence / Distant Recurrence(s)	Disease Status
cCR and nonoperative Surveillance													
1	T2N0	5.5	1.5	APR	cCR	Salvage	APR	pPR	ypT2N0 (0/9), R0	8.2	–	Pelvic	Alive - NED
2	T2N0	2.3	2	APR	cCR	Other[a]	LAR	pCR	ypT0N0 (0/18), R0	22.5	Yes	–	Alive - NED
3	T2N1b	4.5	2	APR	cCR			–	–	31.3	Yes	–	Alive - NED
4	T3N0	3	5	APR	cCR			–	–	31.6	Yes	–	Alive - NED
5	T3N1b	7	4.5	CAA/LAR	cCR			–	–	31.4	Yes	–	Alive - NED
6	T3N1a	6.8	4	LAR	cCR			–	–	29.4	Yes	–	Alive - NED
7	T3N0	7	0	APR	cCR			–	–	28.7	Yes	–	Alive - NED
8	T2N0	3	4	APR	cCR			–	–	28.9	Yes	–	Alive - NED
9	T3N1a	4.2	0	APR	cCR	Salvage	APR	pCR[b]	ypT0N0 (0/9), R0	14.0	Yes	–	Alive - NED
10	T3N1b	4	7	LAR	cCR			–	–	20.2	Yes	–	Alive - NED
11	T3N0	4	6	LAR	cCR			–	–	20.4	Yes	–	Alive - NED
12	T3N2	5	3	APR	cPR-> cCR[c]	Salvage	LAR	pPR	ypT3N0 (0/14), R0	16.6	Yes	–	Alive - NED
13	T2N0	5.5	4	LAR	cCR	Salvage	LAR	pPR	ypT2N0 (0/16), R0	9.4	–	–	Alive - NED
14	T3N1b	2.3	7	LAR	cCR			–	–	21.6	Yes	–	Alive - NED
15	T3N2	4.5	10	LAR	cCR	Salvage	LAR	pPR	ypT3N1 (1/10), R0	17.2	Yes	Pelvic	Alive - NED
cPR: Operative management													
16	T3N0	3.7	3	APR	cPR	Definitive	LAR	pPR	ypT2N0 (0/17), R0	5.6	–	Pelvic	Alive - w/ disease
17	T3N0	8	4	APR	cPR	Definitive	APR	pPR	ypT3N1b (2/13), R0	7.3	–	Pelvic + Distant	Dead - w/ disease
18	T3N1b	6	4.9	APR	cPR	Definitive	APR	pCR[d]	ypT0N0 (0/19)	6.9	–	–	Alive - NED
19	T3N0	3	1	APR	cPR	Definitive	APR	pPR	ypT3N0 (0/11), R0	6.1	–	–	Alive - NED

APR = abdominal perineal resection; CAA = coloanal anastomosis; cCR = clinical complete response; cPR = clinical partial response; ECOG = Eastern Cooperative Oncology Group; LAR = low anterior resection; pCR = pathologic complete response; pPR = pathologic partial response; SD = standard deviation; TME = total mesorectal excision.

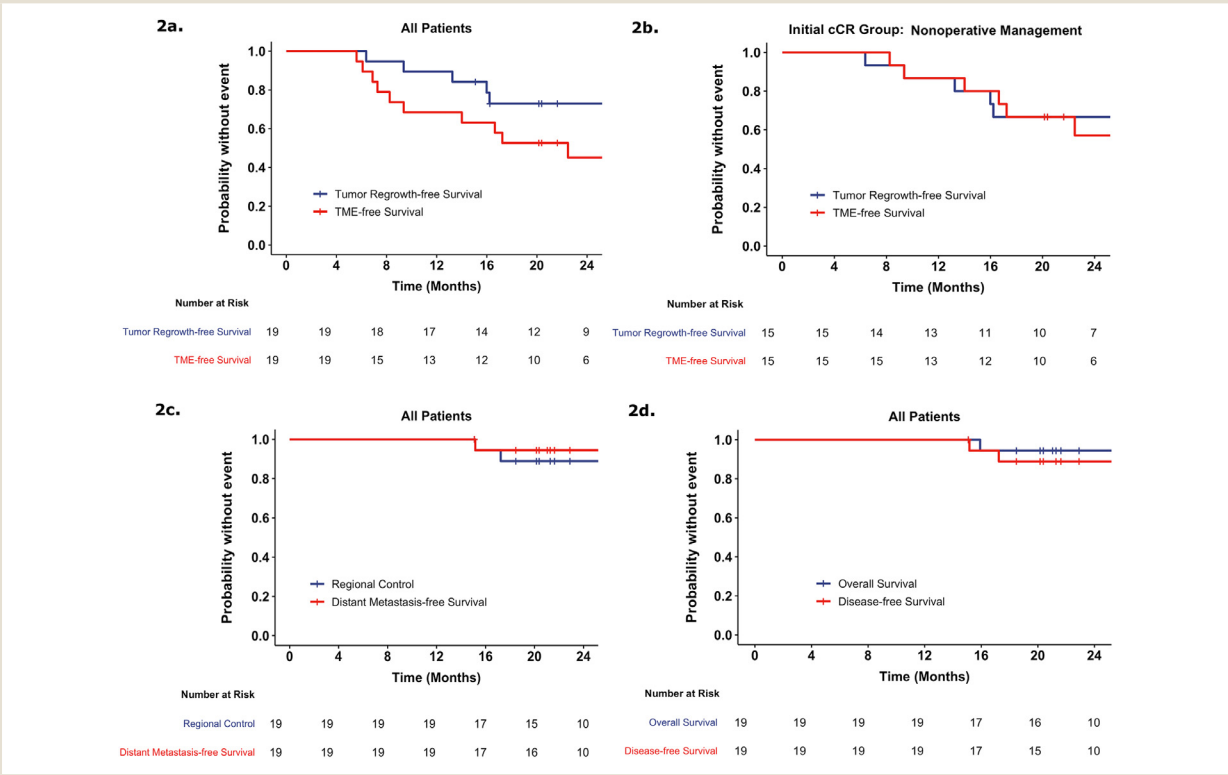
[a] LAR was performed for management of rectosigmoid stricture without clinical evidence of local regrowth.

[b] Patient had pathologically proven local regrowth as seen on transanal resection but had a pCR on subsequent APR.

[c] Patient had an initial cPR after 8 cycles of FOLFOX, but converted to cCR after an additional 3 cycles of FOLFOX and subsequently under nonoperative surveillance.

[d] APR was performed owing to suspected cPR after SC-RT and chemotherapy, but the patient actually had a pCR.

Figure 2 Kaplan-Meier estimates of tumor regrowth-free survival and TME-free survival for (a) all patients and (b) patients with initial cCR. Kaplan-Meier estimates of (c) regional control and distant metastasis-free survival and (d) overall survival and disease-free survival for all patients. cCR = clinical complete response; TME = total mesorectal excision.



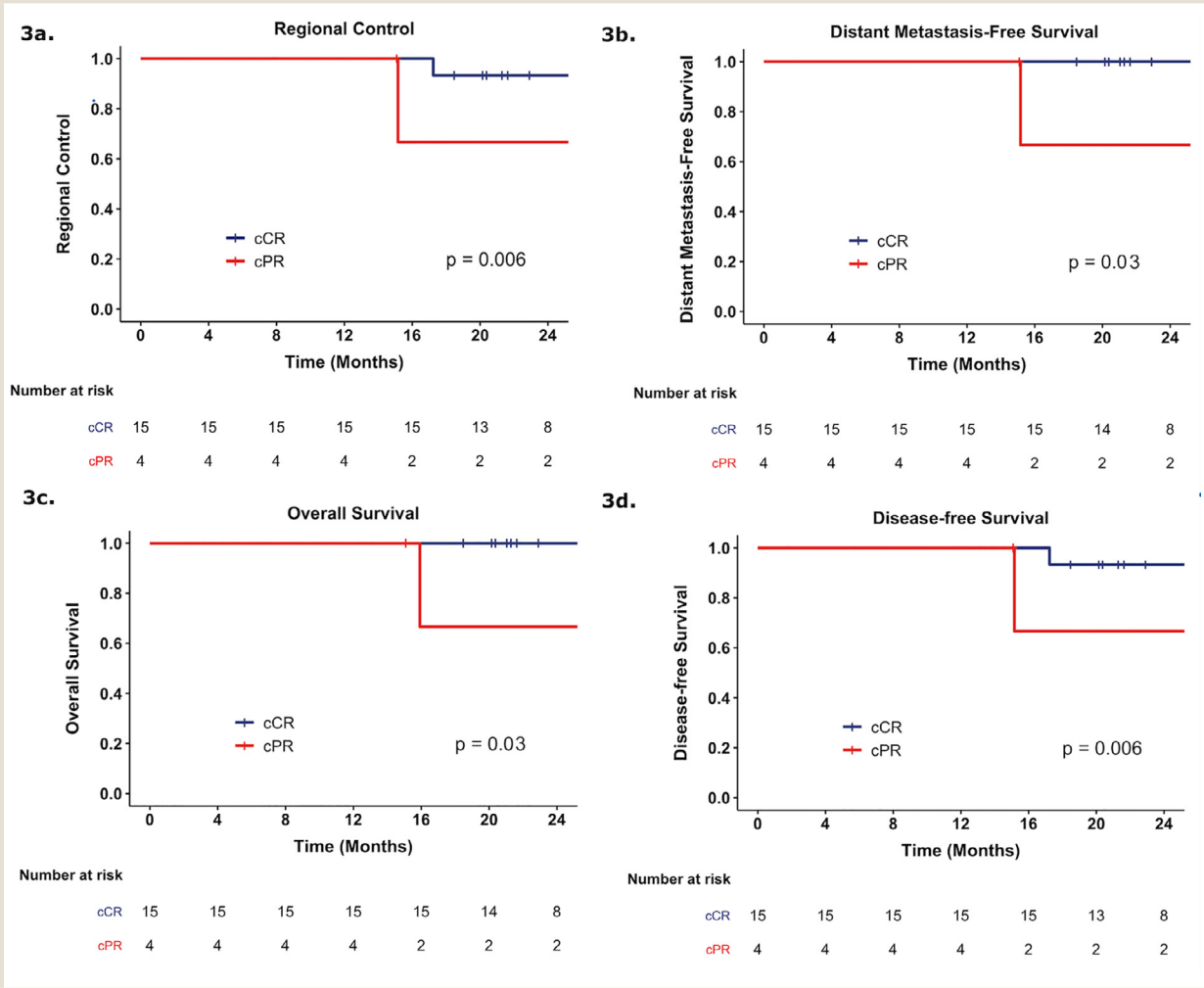
ity was observed in 10 patients (53%) and all occurred during chemotherapy administration. Grade 3 or 4 neutropenia and febrile neutropenia were observed in 5 (26%) and 2 (11%) patients, respectively. There were no grade 5 toxicities. The myocardial infarction observed was likely related to the patient's prior myocardial infarction and the stress of surgery. Importantly, anorectal function by the FACT-C colorectal cancer subscale domain did not differ from baseline. With 89% of ongoing nonoperative patients reporting prediagnosis baseline bowel function, SCRT-CH seems to provide preservation of both organ and function. In this study, 4 of 12 patients (33%) initially deemed to require APR and permanent stoma are undergoing nonoperative management, and 3 of 12 (25%) were able to undergo LAR instead.

With the global coronavirus disease 2019 (COVID-19) pandemic, there is an increasing population of patients with rectal cancer who are treated with SCRT-CH and delayed surgical resection.[11,18–22] With a median TME-free survival of 21.6 months in the nonoperative group, this approach appears to safely delay surgery for these patients with increased risk of mortality owing to COVID-19.[23,24] Further, 5 days of SCRT is significantly fewer outpatient visits than the 28 to 31 visits required for LCCRT. With the recent presentation of the RAPIDO[25] and OPRA[26] studies, there may be an increased interest in SCRT for nonoperative treatment paradigms.

The NORMAL-R study is unique from other SCRT experiences[4,6,25] with 21% of patients having early stage (T2N0) disease. Patients with T2N0 disease were included to allow for treatment of patients with clinically undetectable lymphadenopathy (10%-38%),[27] who may have poorer local control, rectal cancer mortality and OS compared with patients with stage III disease who receive upfront radiation and chemotherapy.[28] Further, even early stage tumors, depending on proximity to sphincter complex and anal verge, can result in a permanent stoma or major LAR syndrome.[2] As more patients are choosing subtherapeutic excisions,[29] despite local excision after LCCRT resulting in a 50% chance of major LAR syndrome,[30] nonoperative paradigms are increasingly important.

The limitations of this study include its small size and the absence of a comparator arm. However, the study was powered appropriately for large differences in outcomes. Multi-institution trials are necessary to validate these findings and are on-going (NCT03904043). Future studies may identify the optimal radiation dose and chemotherapy duration. Additionally, it will be important to evaluate radiographic, biomarker, and circulating tumor DNA correlatives that may predict and prognosticate outcomes. Despite its limitations, this study is the only evidence available demonstrating preliminary safety and efficacy of SCRT-CH,

Figure 3 Comparison of (a) regional control, (b) distant metastasis-free survival, (c) overall survival, and (d) disease-free survival for patients with cCR versus cPR after SCRT and chemotherapy. cCR = clinical complete response; cPR = clinical partial response; SCRT = short-course radiation therapy.



an increasingly implemented treatment paradigm throughout the world.[11,18–22]

Conclusion

These promising data provide timely early evidence that the rapidly adopted regimen of SCRT-CH and nonoperative management for rectal cancer is effective and safe.[18,22] Further investigation of SCRT-CH is warranted.

Clinical Practice Points

- Treatment of locally advanced rectal adenocarcinoma includes radiation therapy, chemotherapy, and surgery.
- SCRT results in decreased disease-related treatment failure and improved pathologic complete response compared with LCCRT.
- Nonoperative management of rectal adenocarcinoma, an increasingly used treatment paradigm (especially during the COVID-19 pandemic), has only been evaluated with LCCRT.
- There are no published data on nonoperative management with curative intent using SCRT.
- In this prospective clinical trial of SCRT followed by chemotherapy, we observed a high initial and 1-year cCR rate of 74% and 68%, respectively.
- Patients with cCR had an improved 2-year disease-free survival, distant metastasis-free survival, and OS compared with patients with a cPR.
- Patient-reported quality of life scores demonstrated no difference in colorectal function at 1 year compared with baseline.
- There were no severe late effects and 89% of patients still undergoing nonoperative management report returning to baseline bowel function.
- These data provide preliminary, prospective evidence that SCRT followed by chemotherapy is safe and effective, with excellent organ function preservation.

• Although limited in study size, these are the only available data evaluating SCRT in the nonoperative setting.

• This is especially critical in the context of a global pandemic, where it is critical to shorten radiation regimens and delay surgeries.

• The recent publication of the RAPIDO study will also increase the use of SCRT.

• Further studies are warranted to explore SCRT in the context of nonoperative management.

Disclosure

The authors have stated that they have no conflicts of interest.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.clcc.2021.03.003.

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