

# Neoadjuvant Chemotherapy, Excision, and Observation for Early Rectal Cancer: The Phase II NEO Trial (CCTG CO.28) Primary End Point Results

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**PURPOSE** Organ-sparing therapy for early-stage I/IIA rectal cancer is intended to avoid functional disturbances or a permanent ostomy associated with total mesorectal excision (TME). The objective of this phase II trial was to determine the outcomes and organ-sparing rate of patients with early-stage rectal cancer treated with neoadjuvant chemotherapy followed by transanal excision surgery (TES).

**METHODS** This phase II trial included patients with clinical T1-T3abN0 low- or mid-rectal adenocarcinoma eligible for endoscopic resection who were treated with 3 months of chemotherapy (modified folinic acid–fluorouracil–oxaliplatin 6 or capecitabine–oxaliplatin). Those with evidence of response proceeded to transanal endoscopic surgery 2–6 weeks later. The primary end point was protocol-specified organ preservation rate, defined as the proportion of patients with tumor downstaging to ypT0/T1N0/X and who avoided radical surgery.

**RESULTS** Of 58 patients enrolled, all commenced chemotherapy and 56 proceeded to surgery. A total of 33/58 patients had tumor downstaging to ypT0/T1N0/X on the surgery specimen, resulting in an intention-to-treat protocol-specified organ preservation rate of 57% (90% CI, 45 to 68). Of 23 remaining patients recommended for TME surgery on the basis of protocol requirements, 13 declined and elected to proceed directly to observation resulting in 79% (90% CI, 69 to 88) achieving organ preservation. The remaining 10/23 patients proceeded to recommended TME of whom seven had no histopathologic residual disease. The 1-year and 2-year locoregional relapse-free survival was, respectively, 98% (95% CI, 86 to 100) and 90% (95% CI, 58 to 98), and there were no distant recurrences or deaths. Minimal change in quality of life and rectal function scores was observed.

**CONCLUSION** Three months of induction chemotherapy may successfully downstage a significant proportion of patients with early-stage rectal cancer, allowing well-tolerated organ-preserving surgery.

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## INTRODUCTION

Organ-sparing therapy for early-stage rectal cancer may avoid a permanent ostomy or functional disturbances, commonly known as low anterior resection syndrome (LARS).<sup>1,2</sup>

Current standard therapy for patients with histologically high-risk clinical (c) T1 and cT2N0 rectal tumors is oncologic resection with total mesorectal excision (TME), combined with preoperative chemoradiation for patients with T3 or N1 tumors.<sup>3</sup> Although locoregional relapse rates with modern neoadjuvant therapy are low and survival is excellent, TME results in issues with bowel function, incontinence, and sexual function. The addition of perioperative radiation can result in LARS in up to 60% of patients.<sup>1,4,5</sup>

Transanal excision surgery (TES) is increasingly used for treatment of select T1N0 or T2N0 rectal tumors.<sup>6,7</sup>

Nonetheless, a significant proportion of cT1-2N0 tumors are pathologically node-positive and there is an increased rate of local relapse with local excision compared with surgical resection.<sup>8-10</sup> Multiple, single-arm and randomized phase II studies exploring the use of pelvic chemoradiation followed by TES in patients with cT1-3 rectal cancer have reported an organ preservation rate of 50%-68%.<sup>11-15</sup> Unfortunately, preoperative radiation significantly increases wound-healing complications<sup>16</sup> and adversely affects sphincter and sexual function.<sup>17</sup>

Neoadjuvant chemotherapy with excision is a potential approach to reduce local and distal relapse of rectal tumors, reducing locoregional recurrence in stage II/III rectal cancer.<sup>18</sup> There is no prospective experience of neoadjuvant chemotherapy and transanal surgery for stage I rectal tumors. The Canadian Cancer Trials Group (CCTG) CO.28 NEO phase II trial was designed to determine the outcomes and organ preservation rate

## CONTEXT

### Key Objective

Can 3 months of modified folinic acid–fluorouracil–oxaliplatin 6 (mFOLFOX6)/capecitabine–oxaliplatin (CAPOX) followed by transanal excision surgery be used to treat magnetic resonance imaging-stage cT1–3bN0 rectal cancer?

### Knowledge Generated

Induction mFOLFOX6/CAPOX followed by transanal excision surgery was well tolerated and resulted in downstaging to ypT0/T1 cN0 tumors in 57% of 58 enrolled patients with well to moderately differentiated adenocarcinoma and preserved mismatch repair. Overall, 79% of patients pursued an organ-sparing strategy, with two patients experiencing a locoregional relapse during the 15.4-month follow-up period. Quality of life and rectal function scores demonstrated almost no change compared with baseline.

### Relevance

Early results suggest that this novel treatment strategy leads to downstaging to ypT0/T1 cN0 in the majority of selected patients with early rectal cancer. The approach offers a much-desired organ-sparing option and warrants further investigation.

of the patients with cT1–T3abN0 rectal tumors treated with chemotherapy (modified folinic acid–fluorouracil–oxaliplatin 6 [mFOLFOX6] or capecitabine–oxaliplatin [CAPOX]) followed by transanal surgery and explore the prognostic value of tumor biomarkers for the outcomes.

## METHODS

### Study Design and Participants

This phase II, nonrandomized, open-label trial accrued adult patients with invasive, well-moderately differentiated rectal adenocarcinoma, stage cT1–T3ab and node-negative (cN0) at seven institutions in Canada and the United States. Patients had low- or mid-rectal tumors by proctoscopy and were deemed eligible for endoscopic resection by the study surgeon. All patients required pelvic magnetic resonance imaging (MRI), computed tomography (CT) scan of the chest, abdomen, and pelvis.

Further criteria included a pretreatment Eastern Collaborative Oncology Group performance score of 0 or 1 and adequate hematologic and organ function. Exclusion criteria included a history of external-beam pelvic radiation, prior therapy for rectal cancer, or metastatic disease.

The study was approved by the site institutional review board, and all patients provided written informed consent to participate.

### Procedures

Patients commenced therapy with six cycles of mFOLFOX6 or four cycles of CAPOX, on the basis of investigator discretion. Each 14-day cycle of mFOLFOX6 consisted of leucovorin 400 mg/m<sup>2</sup> and oxaliplatin 85 mg/m<sup>2</sup> in one 2-hour infusion, bolus fluorouracil 400 mg/m<sup>2</sup> once on day 1, and one 46-hour infusion of fluorouracil 2,400 mg/m<sup>2</sup>. Each 21-day cycle of CAPOX consisted of capecitabine 1,000 mg/m<sup>2</sup> twice daily for 14 days, and oxaliplatin 130 mg/m<sup>2</sup> once on day 1.

Postchemotherapy pelvic MRI and proctoscopy were performed 2–3 weeks after the last dose of chemotherapy. Tumors with protocol-defined evidence of response proceeded to TES. Those with progression or no response to chemotherapy were recommended TME surgery and preoperative pelvic radiation if the MRI revealed cT3ab, cN+, or involved or threatened circumferential radial margin.

TES was performed between 2–6 weeks after the last cycle of chemotherapy. Tumor excision included a minimum of 1-cm gross margin.<sup>19</sup> Trial surgeons had performed at least 20 previous TES procedures for rectal cancer before commencement of the study,<sup>20–22</sup> and each surgeon was required to submit an unedited video of a TES procedure with sutured defect closure for central review. TES could be performed with transanal minimally invasive surgery or transanal endoscopic microsurgery platform or via open transanal excision, per surgeon preference and tumor location.

Local pathology yp (pathologic stage following systemic or radiation therapy prior to surgery) staging review determined subsequent therapy. Patients with yp stage T0/N0 or T1N0 with no poor prognostic features (T1 good) were recommended observation, whereas ypT1 tumors with poor prognostic features, ypT2/3, or any N+ were recommended radical TME surgery. Poor prognostic features included poorly differentiated histology, lymphovascular invasion, and/or positive margin within < 1 mm. Patients assigned to observation were followed for 36 months from the time of TES with proctoscopy every 6 months, pelvic MRI every 6 months (could be substituted with pelvic CT at months 12, 24, and 36), carcinoembryonic antigen every 6 months, and annual contrast CT of the chest, abdomen, and pelvis for 3 years.

Adverse events during chemotherapy were measured using the Common Terminology Criteria for Adverse Events Version 5.0. Perioperative and operative details were collected

prospectively. Quality of life (QoL) and rectal function was assessed using European Organization for Research and Treatment of Cancer Quality of Life Questionnaire–C30, Fecal Incontinence Quality of Life (FIQL),<sup>23</sup> and the LARS surveys.<sup>24</sup> Questionnaires were administered at baseline, pre-excision (postchemotherapy), and 6, 12, 24, and 36 months after tumor surgery.

Molecular profiling was performed on pretreatment formalin-fixed, paraffin-embedded diagnostic biopsies where sufficient tumor was available. If there was inadequate tumor DNA from the diagnostic biopsy, resection specimens were used. Next-generation sequencing (NGS) using the FoundationOne CDx assay was conducted at Foundation Medicine (Cambridge, MA) following standard procedures. This US Food and Drug Administration–approved companion diagnostic provides information on all coding exons from 309 cancer-related genes, fusion identification of 34 commonly rearranged genes, microsatellite instability, and tumor mutation burden (TMB).<sup>25,26</sup>

### Statistical Analysis

The primary end point was protocol-specified organ preservation rate (psOPR), defined as the proportion of patients with tumor downstaging to ypT0/T1goodN0 and who avoided radical surgery. On the basis of the literature published at the time, an organ-preservation rate of 50%–68% would be expected among patients with cT1–3N0 rectal tumors treated with chemoradiation and transanal endoscopic surgery.<sup>11–15</sup> On the basis of this experience, the experimental treatment would be considered of no interest if the psOPR were 50% or lower (H0) and as promising if it were 65% or higher (H1).

The study used a two-stage minimax design with a plan to stop the trial at the end of first stage if  $\leq 10$  of the first 22 patients accrued met the protocol specified criteria of organ preservation. The experimental procedure would be considered as promising if, out of the total patients accrued, 30 or more met the protocol specified criteria of organ preservation. The type-I error rate and power of this design was 0.1 and 0.8, respectively. Minimum and maximum sample sizes, respectively, were 22 and 50 evaluable patients. Allowing for up to 15% of patients who may not commence neoadjuvant chemotherapy and be treated with surgery and thus be considered as inevaluable, the total sample size was 58 patients.

The psOPR was estimated using the intention-to-treatment principle for all patients completing neoadjuvant chemotherapy. Because of the observation that a high proportion of patients declined protocol recommended surgery, the observed organ preservation rate (oOPR) was defined at the time of data analysis, representing the proportion of patients downstaged to ypT0/T1 *plus* higher yp stage patients who declined recommended TME surgery. Exact Clopper-Pearson confidence intervals were calculated for both psOPR and oOPR. Kaplan-Meier method was used to

estimate 1- and 2-year locoregional relapse-free survival, from the date of enrollment. Patients were censored at latest date of last date of distant relapses (for locoregional relapse-free survival only), date of death, date of lost to follow-up, and last disease assessment date.

Adverse events were analyzed for treated patients. The means of QoL and rectal function scales at each time point were calculated. European Organization for Research and Treatment of Cancer Quality of Life Questionnaire–C30 functioning and global scales were scored from 0 to 100, with higher scores indicating better QoL. FIQL was scored with a range from 1 to 5, with 1 indicating a lower functional

**TABLE 1.** Characteristics of 58 Patients Enrolled in the Study

Characteristic	N = 58
Age, years	
Median	67
Range	31–83
Sex, No. (%)	
Male	41 (71)
Female	17 (29)
Race, No. (%)	
White	48 (83)
Indigenous	6 (10)
Asian	4 (7)
ECOG, No. (%)	
0	47 (81)
1	11 (19)
Histology, No. (%)	
Adenocarcinoma, well/moderately differentiated	58 (100)
Mismatch repair status, No. (%)	
pMMR	55 (95)
Unknown	3 (5)
cT by MRI, No. (%)	
T1	8 (14)
T2	37 (64)
T3a/b	10/3 (22)
cN by MRI, No. (%)	
cN0	58 (100)
Tumor distance from anal verge, cm	
Median	6
Range	0–18
Mutational profile (n = 53), No. (%)	
RAS-mutated	33 (60)
BRAF V600E-mutated	0 (0)
ERBB2-amplified	3 (6)

Abbreviations: c, clinical; ECOG, Eastern Cooperative Oncology Group; MRI, magnetic resonance imaging; N, node; pMMR, preserved mismatch repair; T, tumor.

status of QoL.<sup>23</sup> Proportion of patients with LARS scores in the following validated categories was calculated at each time point: 0-20 no LARS, 21-29 minor LARS, and 30-42 major LARS.<sup>24</sup> The prognostic value of *RAS*, the main variable of interest in genomic analyses, was evaluated by a Fisher's exact test with a comparison of the psOPR between patients with mutated and wild-type *RAS*.

The study was conducted by the Canadian Cancer Trials Group with support from the Canadian Cancer Society. The trial is registered with ClinicalTrials.gov (identifier: [NCT03259035](https://clinicaltrials.gov/ct2/show/study/NCT03259035)).<sup>27</sup>

## RESULTS

The study opened to accrual on August 22, 2017. After enrollment of the initial 22 patients, the interim efficacy analysis on April 19, 2019, documented that > 50% of patients avoided radical surgery, allowing full accrual to be completed on May 19, 2020. The results presented are based on database lock from January 20, 2021, and a median follow-up of 15.4 months. A total of 58 eligible patients were accrued in Canada and the United States and characteristics are summarized in [Table 1](#). Patients had a median age of 67 years, 71% were male, and all had well-moderately differentiated, nonmucinous rectal adenocarcinoma. Most common MRI cT-stage was T2 (64%), and the median tumor height was 6.0 (range, 0-18) cm.

### Chemotherapy

All 58 enrolled patients commenced either mFOLFOX6 (32) or CAPOX (26) of which 91% and 89%, respectively, completed all planned cycles. Oxaliplatin relative dose intensity (RDI) was  $\geq 90\%$  in 59%, 80% to < 90% in 22%,

and 60%-80% in 19%. Infusional 5-fluorouracil RDI was  $\geq 90\%$  in 53%, 80% to < 90% in 22%, and 60%-80% in 19%, whereas RDI for capecitabine was reduced at 80% to < 90% in 50%, 60% to < 80% in 22%, and < 60% in 19%. There were no unexpected toxicities; the most common grade 3/4 adverse events are summarized in [Table 2](#), and there were no grade 5 events.

### Surgical Therapy

Among 58 patients who commenced chemotherapy, 56 proceeded to TES by transanal minimally invasive surgery/transanal endoscopic microsurgery (53), or open local excision (three), of whom 52 (93%) had an R0 excision, two (3.5%) were R1, and two (3.5%) R2. Of the 56 patients who had a tumor excision, 10 proceeded to subsequent protocol-recommended TME surgery on the basis of residual ypT2+ and/or R1/2 tumor in the excision specimen. Morbidity of TES and TME surgeries was low ([Table 2](#)).

Two of the 58 enrolled patients did not proceed to TES after completion of chemotherapy. One, who had an initial cT1N0 tumor and developed progression to cT3b on imaging after chemotherapy, proceeded directly to TME surgery. TME pathologic specimen showed ypT2N0 with a negative circumferential margin. The second patient with initial cT2N0 tumor had no chemotherapy response, and was treated with pelvic chemoradiation at standard doses with a clinical tumor response and scheduled for organ-sparing TES because of patient preference.

### Organ Preservation

The psOPR is presented in an intention-to-treat analysis in [Table 3](#). A total of 33/58 patients had tumor downstaging to ypT0/1N0/X on the TES specimen, resulting in a psOPR of 57% (90% CI, 45 to 68). The psOPR was similar among T stage subgroups and was 63% (n = 8), 54% (n = 37), and 62% (n = 13) in cT1, T2, and T3ab groups, respectively. Of 23 remaining patients recommended for TME surgery on the basis of protocol requirements, 13 declined and elected to proceed directly to observation resulting in an oOPR of 46/58 (79% with 90% CI, 69 to 88). The yp tumor stage on TES specimen of the 13 patients who declined TME was T1 with histologic high-risk features in one patient, T2 in 11 patients, and T3 in one patient. The final TME specimen yp stage of the 10 patients who proceeded to surgery is provided ([Table 3](#)), of whom seven had no pathologically residual disease.

### Summary of Therapy

Treatment of all enrolled patients is summarized in a flow diagram in [Figure 1](#). During the follow-up period, two locoregional recurrences were documented, one in a patient who declined protocol recommended TME surgery. Both were initially diagnosed with MRI-stage cT2, low-lying tumors at enrollment. One had residual ypT2, whereas the other had ypT1 on TES specimen after induction

**TABLE 2.** Summary of Chemotherapy and Surgery Adverse Events

Chemotherapy		
Adverse Events	Grade 3, No. (%)	Grade 4, No. (%)
Blood and lymphatic system	1 (2)	0
Biochemistry (creatinine clearance)	0	3 (5)
Hematologic	5 (9)	4 (7)
GI	13 (22)	1(2)
Musculoskeletal	2 (3)	0
TES and TME surgery		
Adverse Events	TES (n = 56)	TME (n = 10)
Estimated blood loss, cc (range)	5 (0-300)	65 (10-3,000)
Transfusion, No. (%)	0	2 (20)
Intraoperative injury, No. (%)	1 (2)	2 (20)
Need for intensive care unit, No. (%)	1 (2)	2 (20)
Median hospitalization LOS, days (range)	0 (0-2)	5 (4-17)
Operative mortality	0	0

Abbreviations: LOS, length of stay; TES, transanal excision surgery; TME, total mesorectal excision.

**TABLE 3.** Clinical Stage, psOPR, and Pathologic Outcomes of Patients Treated With TES or TME Surgery

cT Stage	TES ypT Status, NO/X				psOPR, No. (%)	TME ypT Status				TME ypN Status	
	T0	T1	T2	T3		T0	T1	T2	T3	N0	N1
T1 (n = 8)	3	2	1	1	5/8 (63)	1	0	0	0	1	0
T2 (n = 37)	10	10	16	0	20/37 (54)	4	0	0	2	5	1
T3 (n = 13)	7	2 <sup>a</sup>	3	1	8/13 (62)	3	0	0	0	2	1
Totals (N = 58)	20	14	20	2	33/58 (57)	8	0	0	2	8	2
	TES = 56				90% CI, 45 to 68	TME = 10					

Abbreviations: c, clinical; N, node; psOPR, protocol specified organ preservation rate; T, tumor; TES, transanal excision surgery; TME, total mesorectal excision; yp, pathologic stage following systemic or radiation therapy prior to surgery.

<sup>a</sup>Includes one (1) patient with pT1 pathologic high-risk features recommended for TME.

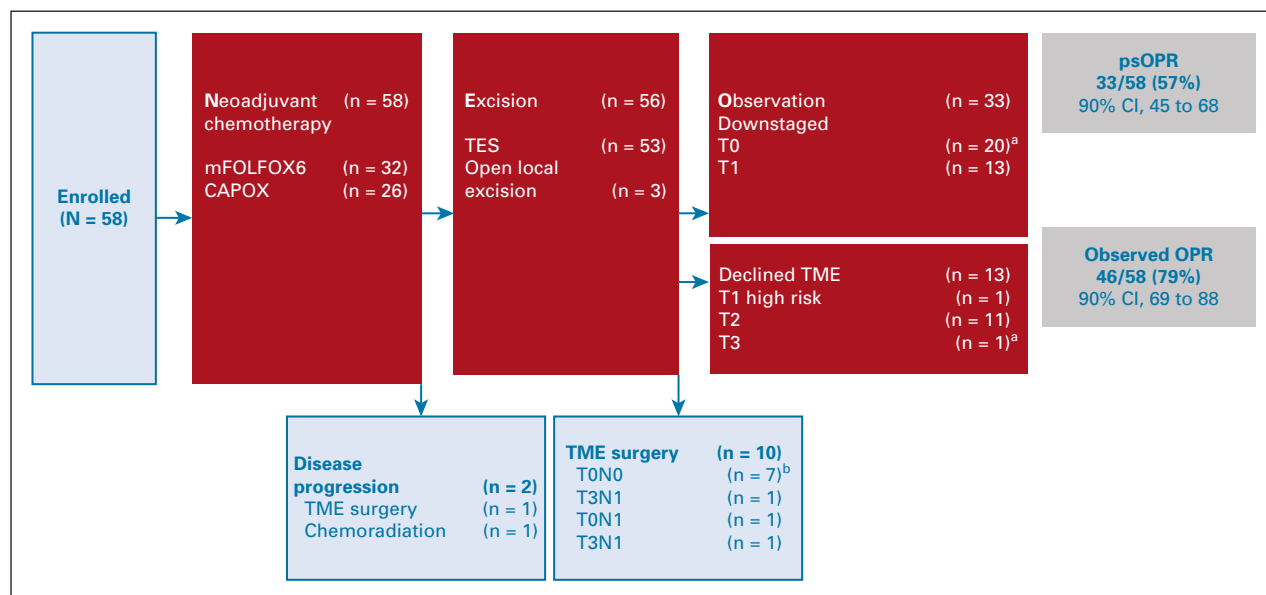
chemotherapy. The 1-year and 2-year locoregional relapse-free survival rates were, respectively, 98% (95% CI, 86 to 100) and 90% (95% CI, 58 to 98; see Appendix Fig A1 [online only]). There were no distant recurrences or deaths.

### Tumor Genotyping

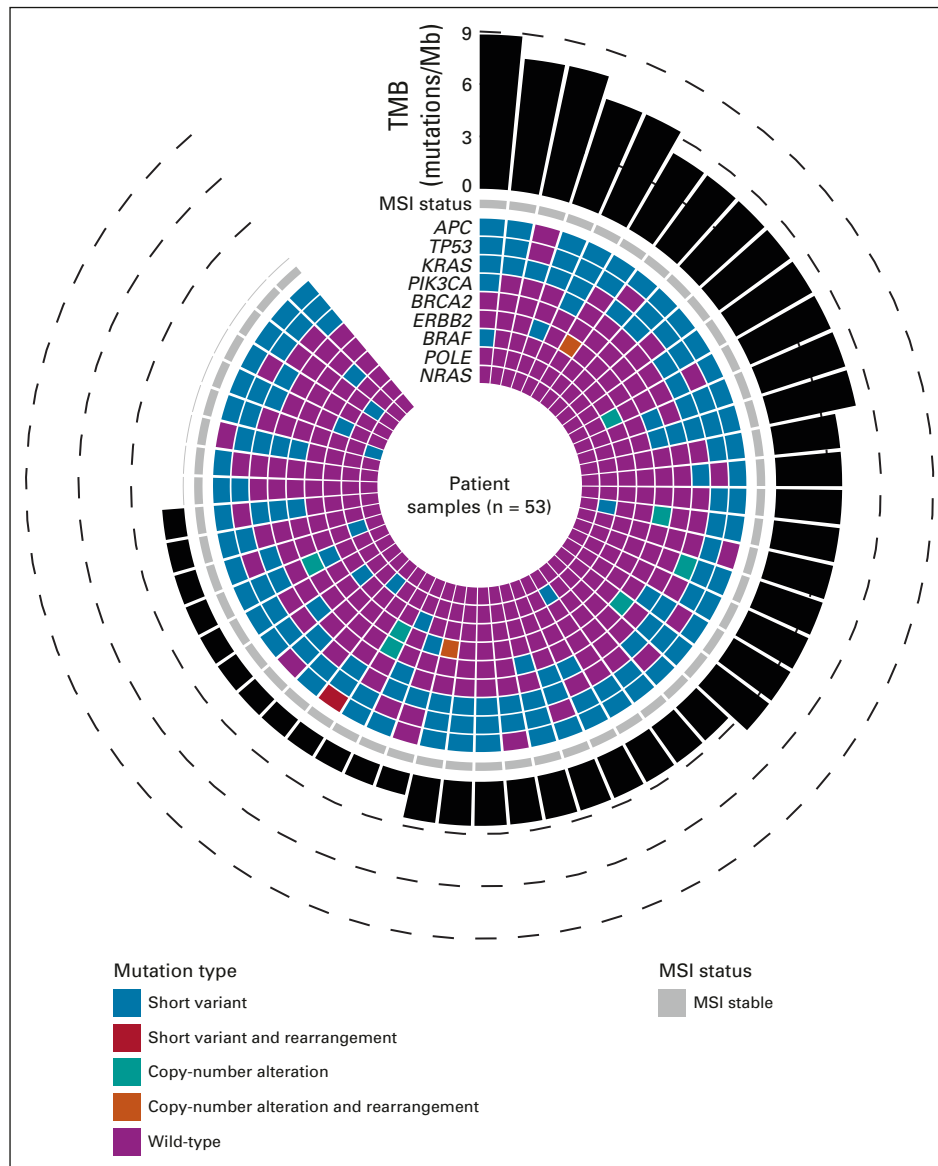
Tumor genotyping with FoundationOne CDx was done for 53/58 patients with sufficient tissue. Median TMB (interquartile range) was 2.52 mutations/Mb (1.26-5.04) in the 48 patients with TMB available, and the frequency of the most common variants is provided in Figure 2 for 53 patients with sufficient tissue for NGS. There was no association between *RAS* mutation status and tumor downstaging after mFOLFOX6/CAPOX chemotherapy with a total of 16/33 (49%) of *RAS*-mutant tumors downstaged to ypT0/1 compared with 12/20 (60%) in the *RAS* wild-type group,  $P = .57$ . No *BRAF* V600E mutations were noted.

MMR status was available in 55/58 patients on the basis of immunohistochemistry (IHC) or NGS assay. 55/55 (100%) were pMMR, and concordance between IHC and NGS was 30/30 (100%) in patients with overlapping assays. *ERBB2* amplification was noted in 3/53 patients (5.7%), with all three showing tumor downstaging and a psOPR of 67%.

Compliance with all QoL and rectal function instruments was 100% at baseline, 89% pre-excision, 85% at 6 months, and 86% at 12 months (Figs 3A-3C). At baseline, the proportion of patients with major LARS was 10%. No patient had major LARS at pre-excision visit. The proportion of patients with major LARS was 22% at 6 months postexcision and was decreased to 14% at 12 months. Total mean LARS scores are provided in Figure 3B. At all time points, there was almost no change from baseline for FIQL lifestyle and depression/self-perception scales (Fig 3C).



**FIG 1.** Flow diagram of 58 patients enrolled in the study. <sup>a</sup>Represents ypT, cN0 stage. <sup>b</sup>Represents yp stage. c, clinical; CAPOX, capecitabine-oxaliplatin; mFOLFOX, modified folinic acid-fluorouracil-oxaliplatin 6; N, node; oOPR, observed organ preservation rate; psOPR, protocol-specified organ preservation rate; T, tumor; TES, transanal excision surgery; TME, total mesorectal excision; yp, pathologic stage following systemic or radiation therapy prior to surgery.



**FIG 2.** Tumor genotype by FoundationOne CDx analysis in 53 patients with sufficient archival tumor tissue. MSI, microsatellite; TMB, tumor mutation burden.

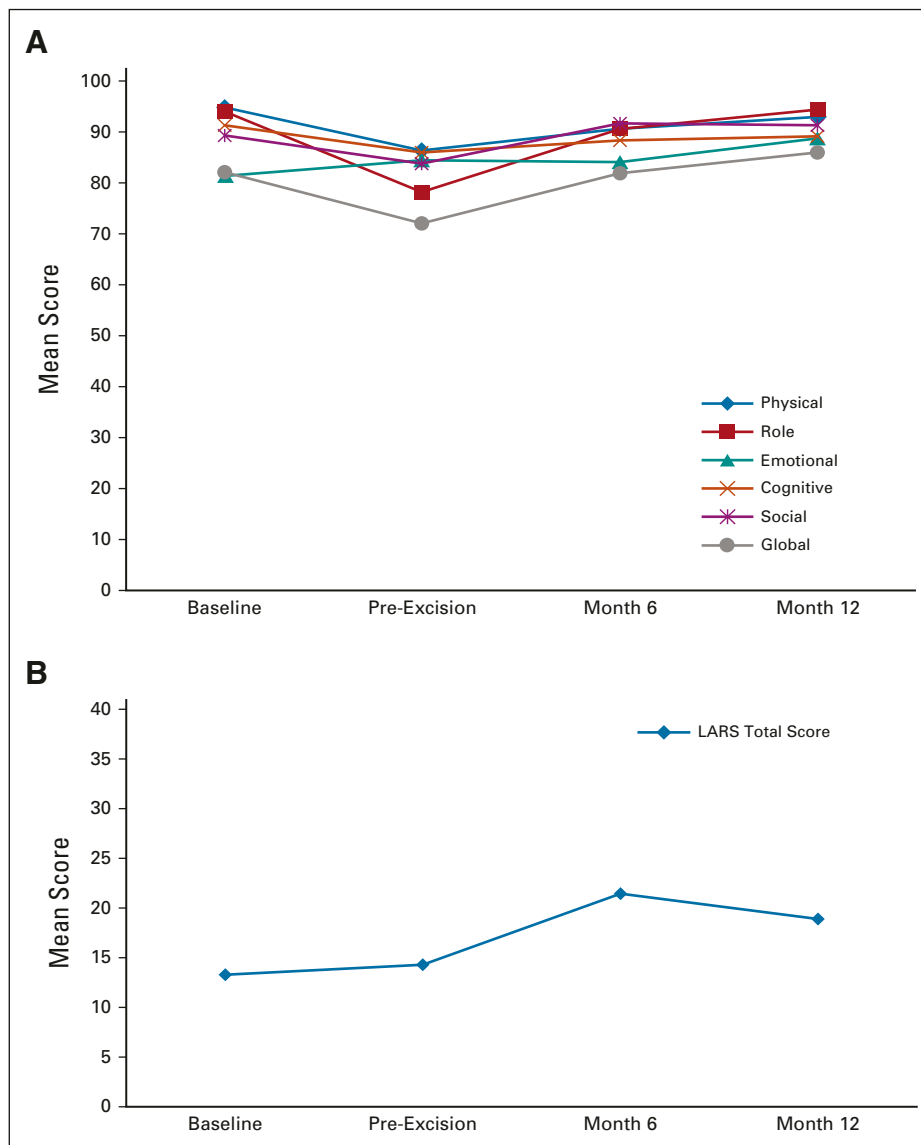
The video presentation of the study results presented at Virtual ASCO 2021 are provided in the Data Supplement (online only).

## DISCUSSION

To our knowledge, this is the first published study to describe organ-sparing outcomes of patients with stage I and early-stage II rectal cancer treated with induction chemotherapy and transanal surgical excision. More than half of the enrolled patients experienced complete or near-complete pathologic downstaging and met the protocol criteria for organ-sparing therapy. A significantly larger proportion of patients chose to defer recommended TME surgery in favor of close observation on study. No unexpected toxicities were encountered.

Study results compare favorably to prior organ-sparing studies using standard chemoradiation before TES, including the CARTS trial, in which 55% of 55 patients with low T1-T3abN0 rectal tumors achieved tumor downstaging to ypT0/1.<sup>13,14</sup> In the ACOSOG Z6041, downstaging to ypT0/T1 was achieved in 64% of 77 patients with cT2N0 tumors treated with chemoradiation with capecitabine and oxaliplatin,<sup>12</sup> whereas in the GRECCAR2 trial, 64% (n = 74) of patients with cT2-3/N0-1 tumors downstaged to ypT0/1,<sup>15</sup> and Lezoche et al<sup>11</sup> reported 52% of cT2N0 tumors (n = 100) were ypT0/1 stage after chemoradiation.

The oOPR was 79%, including patients who declined recommended surgery, and may reflect the patient preference to avoid radical surgery despite a higher risk of locoregional



**FIG 3.** (A) EORTC QLQ-C-30 scores at baseline, pre-excision, 6 months, and 12 months after TES. Functioning and global scales were scored from 0 to 100, with higher scores indicating better QoL. Observed/expected sample size was 58/58 at baseline, 53/58 at pre-excision, 37/43 at 6 months after TES, and 23/26 at 12 months after TES. (B) LARS mean total scores at baseline, pre-excision, 6 months, and 12 months after excision. Scores of 0-20 correspond to no LARS, 21-29 to minor LARS, and 30-42 to major LARS. Observed/expected sample size was 58/58 baseline, 50/58 pre-excision, 36/43 at 6 months after TES, and 21/26 at 12 months after TES. (C) FIQL mean scores at baseline, pre-excision, 6 months, and 12 months after excision. FIQL was scored with a range from 1 to 5 with 1 indicating a lower functional status of QoL. Observed/expected sample size was 52/58 at baseline, 52/58 at pre-excision, 37/43 at 6 months after TES, and 23/26 at 12 months after TES. EORTC QLQ-C-30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30; FIQL, Fecal Incontinence Quality of Life; LARS, Low Anterior Resection Syndrome; QoL, quality of life; TES, transanal excision surgery. (continued on following page)

recurrence. This choice in favor of an organ-sparing approach is similar to trends observed in other prospective studies.<sup>11,13,14</sup> Among the 13 patients who declined recommended TME, 85% had ypT2N0 tumors and one patient developed a locoregional relapse during the follow-up period

that was successfully resected with a TME. Among the 10 patients who proceeded to recommended TME surgery, only two had pathologically N1 tumors (Table 3), a rate similar to the expected node-positive rate of pT2 tumors described in prior literature.<sup>8-10</sup>

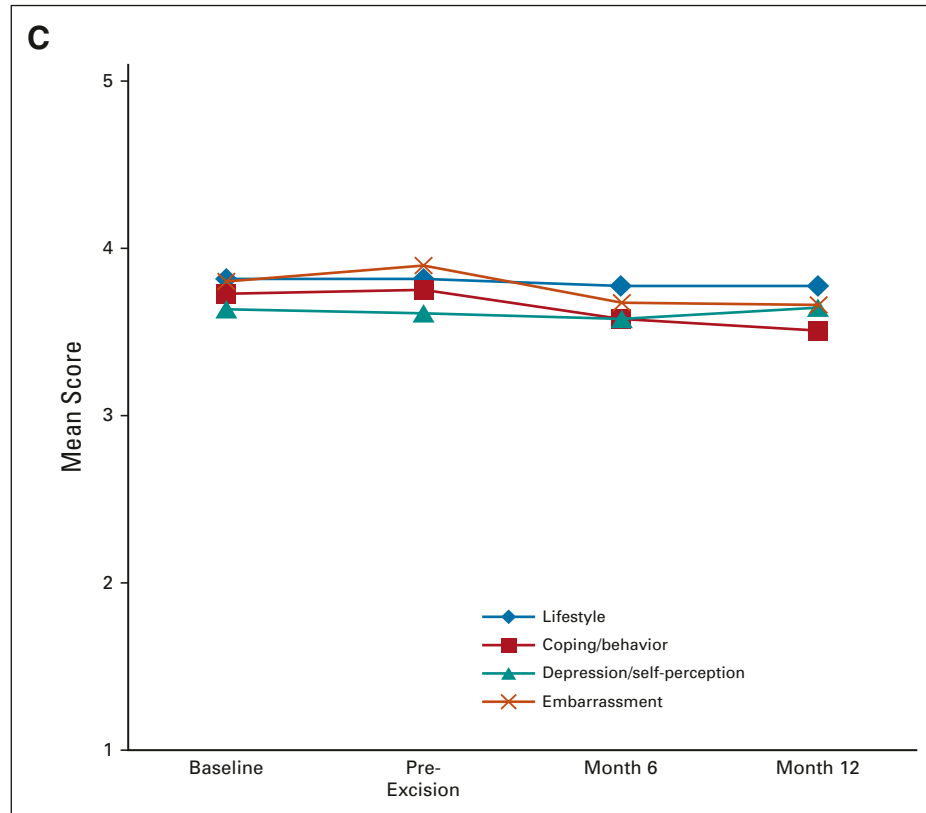


FIG 3. (Continued).

Only one of 58 patients enrolled was treated with pelvic chemoradiation in this study. This patient had no response to chemotherapy documented by pre-excision MRI and endoscopy; however, a significant tumor response was achieved after subsequent standard long-course chemoradiation, after which the patient was eligible for organ-sparing TES.

In this protocol, surgery followed chemotherapy, in contrast to the watch-and-wait approach according to previous published criteria used for stage II/III rectal tumors.<sup>28</sup> This study demonstrates the important role played by TES in accurately documenting the residual tumor burden, thereby informing provider and patient decision making about the need of subsequent therapy. In the 13/56 (23%) of patients who underwent TES with a resultant ypT1 tumor, transanal surgery removed microscopic residual disease that may otherwise have been difficult to differentiate from a clinical complete response on proctoscopy and MRI. Furthermore, recent work suggests TES can enhance the opportunity for organ preservation even in patients with locally advanced disease who achieve a near-complete response.<sup>29</sup>

In this study, there were very few postoperative complications and no patients required readmission after TES. The early QoL results suggest that TES had only minor effects on bowel function, which subsequently improved.

This is in line with prior published reports that anal manometric values return to normal by 6-12 months, and continence scores back to normal by 1 year in TES patients.<sup>30</sup> In this study, mean LARS score increased to minor LARS 6 months after excision and improved by the 12-month time point to no LARS, similar to baseline. Minimal change in fecal incontinence scores was noted on the FIQL questionnaire.

Molecular testing for biomarkers was successfully done on most patients. The common alteration, *RAS* mutation, was not associated with response to chemotherapy. Tumors had preserved mismatch repair, a low mutation burden, and no *BRAF V600E* mutations, characteristic of the majority of left-sided colorectal tumors.<sup>31</sup> *ERBB2* gene amplification was documented in 6% of tumors (three) having a yp stage of T0, T1, and T2 after chemotherapy. Given the small number of patients with this alteration, it is difficult to make any firm statements about predictive efficacy in this population.

The study included patients with MRI-staged early rectal cancer with no unfavorable histologic characteristics. A larger, hypothesis-confirming study is required in this patient population. Patients were treated at cancer centers specialized in rectal cancer diagnosis, therapy, and transanal surgery. This concentration of rectal cancer surgery at higher-volume centers has been previously described<sup>32</sup> with consequent superior outcomes in the setting of organ-sparing



therapy. The American College of Surgeons (2014) created the National Accreditation Program for Rectal Cancer structured around evidence-based and a multidisciplinary team approaches,<sup>33</sup> a strategy enabling patients to benefit from novel approaches such as NEO.

In conclusion, three months of induction chemotherapy with mFOLFOX6/CAPOX may successfully downstage a significant proportion of patients with favorable-risk, early-stage rectal cancer, allowing well-tolerated organ-preserving surgical therapy with minimal effect on organ function.

## AFFILIATIONS

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#### AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

##### Neoadjuvant Chemotherapy, Excision, and Observation for Early Rectal Cancer: The Phase II NEO Trial (CCTG CO.28) Primary End Point Results

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Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians ([Open Payments](#)).

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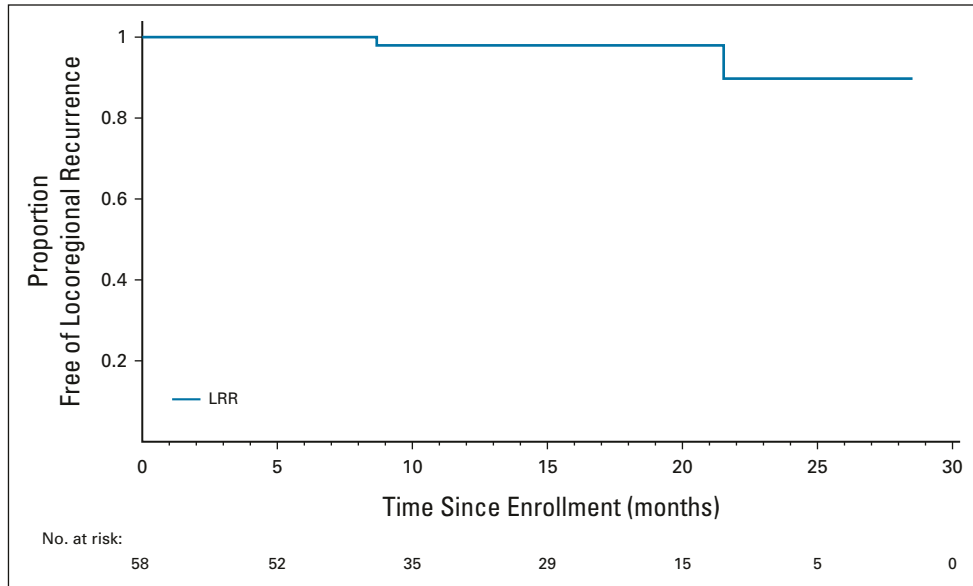
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## APPENDIX



**FIG A1.** Kaplan-Meier curve for LRR-free survival among 58 patients enrolled in the study. LRR, locoregional recurrence.