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William C. Chapman

Hyun Kim

Philip Bauer

Bilal A. Makhdoom

Nikolaos A. Trikalinos

See next page for additional authors

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Authors

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ORIGINAL CONTRIBUTION

Total Neoadjuvant Therapy With Short-Course Radiation: US Experience of a Neoadjuvant Rectal Cancer Therapy

William C. Chapman Jr., M.D., M.P.H.S.[1] • Hyun Kim, M.D.[2] • Philip Bauer, M.D.[1]
Bilal A. Makhdoom, B.A.[1] • Nikolaos A. Trikalinos, M.D., M.S.[3] • Katrina S. Pedersen, M.D.[3]
Sean C. Glasgow, M.D.[1] • Matthew G. Mutch, M.D.[1] • Matthew L. Silviera, M.D.[1]
Amit Roy, M.D.[2] • Parag J. Parikh, M.D.[4] • Steven R. Hunt, M.D.[1]

1 Department of Surgery, Section of Colon and Rectal Surgery, Washington University School of Medicine, St. Louis, Missouri
2 Department of Radiation Oncology, Washington University School of Medicine, St. Louis, Missouri
3 Department of Medicine, Division of Medical Oncology, Washington University School of Medicine, St. Louis, Missouri
4 Department of Radiation Oncology, Henry Ford Cancer Institute, Detroit, Michigan

BACKGROUND: Short-course radiation followed by chemotherapy as total neoadjuvant therapy has been investigated primarily in Europe and Australia with increasing global acceptance. There are limited data on this regimen's use in the United States, however, potentially delaying implementation.

OBJECTIVE: This study aimed to compare clinical performance and oncologic outcomes of 2 rectal cancer neoadjuvant treatment modalities: short-course total neoadjuvant therapy versus standard chemoradiation.

DESIGN: This is a retrospective cohort study.

SETTING: This study was performed at a National Cancer Institute-designated cancer center.

PATIENTS: A total of 413 patients had locally advanced rectal cancers diagnosed from June 2009 to May 2018 and received either short-course total neoadjuvant therapy or standard chemoradiation.

INTERVENTIONS: There were 187 patients treated with short-course total neoadjuvant therapy (5 × 5 Gy radiation followed by consolidation oxaliplatin-based chemotherapy) compared with 226 chemoradiation recipients (approximately 50.4 Gy radiation in 28 fractions with concurrent fluorouracil equivalent).

MAIN OUTCOME MEASURES: Primary end points were tumor downstaging, measured by complete response and "low" neoadjuvant rectal score rates, and progression-free survival. Secondary analyses included treatment characteristics and completion, sphincter preservation, and recurrence rates.

RESULTS: Short-course total neoadjuvant therapy was associated with higher rates of complete response (26.2% vs 17.3%; $p = 0.03$) and "low" neoadjuvant rectal scores (40.1% vs 25.7%; $p < 0.01$) despite a higher burden of node-positive disease (78.6% vs 68.9%; $p = 0.03$). Short-course recipients also completed trimodal treatment more frequently (88.4% vs 50.4%; $p < 0.01$) and had fewer months with temporary stomas (4.8 vs 7.0; $p < 0.01$). Both regimens achieved comparable local control (local recurrence: 2.7% short-course total neoadjuvant therapy vs 2.2% chemoradiation, $p = 0.76$) and 2-year progression-free survival (88.2% short-course total neoadjuvant therapy (95% CI, 82.9–93.5) vs 85.6% chemoradiation (95% CI, 80.5–90.7)).

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Correspondence: William C. Chapman Jr., M.D., M.P.H.S., Washington University School of Medicine, Department of Surgery, Campus Box 8109, 660 S Euclid Ave, St. Louis, MO 63110. E-mail: chapmanjr@wustl.edu

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LIMITATIONS: Retrospective design, unbalanced disease severity, and variable dosing of neoadjuvant consolidation chemotherapy were limitations of this study.

CONCLUSIONS: Short-course total neoadjuvant therapy was associated with improved downstaging and similar progression-free survival compared with chemoradiation. These results were achieved with shortened radiation courses, improved treatment completion, and less time with diverting ostomies. Short-course total neoadjuvant therapy is an optimal regimen for locally advanced rectal cancer. See **Video Abstract** at http://links.lww.com/DCR/B724.

TERAPIA NEOADYUVANTE TOTAL CON RADIACIÓN DE CORTA DURACIÓN: EXPERIENCIA ESTADOUNIDENSE DE UNA TERAPIA NEOADYUVANTE CONTRA EL CÁNCER DE RECTO

ANTECEDENTES: La radiación de corta duración seguida de quimioterapia como terapia neoadyuvante total se ha investigado principalmente en Europa y Australia con una aceptación mundial cada vez mayor. Sin embargo, datos limitados sobre el uso de este régimen en los Estados Unidos, han potencialmente retrasando su implementación.

OBJETIVO: Comparar el desempeño clínico y los resultados oncológicos de dos modalidades de tratamiento neoadyuvante del cáncer de recto: terapia neoadyuvante total de corta duración versus quimioradiación. estándar.

DISEÑO: Cohorte retrospectivo.

AJUSTE: Centro oncológico designado por el NCI.

PACIENTES: Un total de 413 cánceres rectales localmente avanzados diagnosticados entre junio de 2009 y mayo de 2018 que recibieron cualquiera de los regímenes neoadyuvantes.

INTERVENCIONES: Hubo 187 pacientes tratados con terapia neoadyuvante total de ciclo corto (radiación 5 × 5 Gy seguida de quimioterapia de consolidación basada en oxaliplatino) en comparación con 226 pacientes de quimiorradiación (aproximadamente 50,4 Gy de radiación en 28 fracciones con equivalente de fluorouracilo concurrente).

PRINCIPALES MEDIDAS DE RESULTADO: Los criterios primarios de valoración fueron la disminución del estadio del tumor, medido por la respuesta completa y las tasas de puntuación rectal neoadyuvante "baja", y la supervivencia libre de progresión. Los análisis secundarios incluyeron las características del tratamiento y las tasas de finalización, conservación del esfínter y recurrencia.

RESULTADOS: La terapia neoadyuvante total de corta duración, se asoció con tasas más altas de respuesta completa (26,2% versus 17,3%, $p = 0,03$) y puntuaciones rectales neoadyuvantes "bajas" (40,1% versus 25,7%, $p < 0,01$) a pesar de una mayor carga de enfermedad con ganglios positivos (78,6% versus 68,9%, $p = 0,03$). Los pacientes de ciclo corto también completaron el tratamiento trimodal con mayor frecuencia (88,4% versus 50,4%, $p < 0,01$) y tuvieron menos meses con estomas temporales (4,8 versus 7,0, $p < 0,01$). Ambos regímenes lograron un control local comparable (recidiva local: 2,7% de SC-TNT versus 2,2% de TRC, $p = 0,76$) y supervivencia libre de progresión a 2 años (88,2% de SC-TNT [IC: 82,9 - 93,5] versus 85,6% CRT [CI: 80,5 - 90,7]).

LIMITACIONES: Diseño retrospectivo, gravedad de la enfermedad desequilibrada y dosificación variable de quimioterapia neoadyuvante de consolidación.

CONCLUSIONES: La terapia neoadyuvante total de ciclo corto se asoció con una mejora en la reducción del estadio y una supervivencia libre de progresión similar en comparación con la quimioradiación. Estos resultados se lograron con ciclos de radiación más cortos, tratamientos mejor finalizados y menos tiempo en ostomías de derivación. La terapia neoadyuvante total de corta duración es un régimen óptimo para el cáncer de recto localmente avanzado. Consulte **Video Resumen** en http://links.lww.com/DCR/B724. (*Traducción- Dr. Fidel Ruiz Healy*)

KEY WORDS: Neoadjuvant therapy; Rectal cancer; Short-course radiation; Total neoadjuvant therapy.

Locally advanced rectal cancer has traditionally been treated with neoadjuvant chemoradiation therapy (CRT), surgery, and adjuvant chemotherapy in the United States. Within the past decade, however, multiple reports have described a promising new strategy, termed total neoadjuvant therapy (TNT). Early regimens, predominately composed of induction chemotherapy followed by CRT, have achieved higher trimodal therapy completion rates and better tumor downstaging than traditional therapy.[1,2]

However, TNT regimens that include consolidation instead of induction chemotherapy[3] or replace CRT with short-course (5 × 5 Gy) radiation[4,5] have also shown early promise and offer unique advantages. In particular, short-course radiation reduces overall treatment duration, patient burden, and costs by cutting radiation fractions from 28 to 5.[6] In this environment, European consensus guidelines now recommend a TNT approach incorporating short-course radiotherapy.[7] Despite these potential advantages, the implementation of short-course radiation and TNT in North America has been rare.[8]

Since 2016, short-course radiation with TNT (SC-TNT) has been the standard neoadjuvant regimen for locally advanced rectal cancer at Washington University. Based on anecdotal clinical experience and limited phase II data,[5] we hypothesized that SC-TNT would be associated with increased tumor downstaging, longer progression-free survival, and fewer fractions of radiation. Herein, we report the clinical performance metrics and early oncologic outcomes of an SC-TNT regimen utilized at our center during the past decade.

METHODS

Study Population

Patients with locally advanced rectal cancer who underwent neoadjuvant CRT or SC-TNT at our National Cancer Institute-designated cancer center from June 2009 to May 2018 were selected for inclusion in this retrospective cohort study. We defined locally advanced rectal cancer as biopsy-proven adenocarcinoma located within 15 cm of the anal verge on digital or rigid proctoscopic examination with clinical staging of T3/T4 N0 or T(any) N+.[9] Local staging was accomplished by endorectal ultrasound or MRI, whereas CT of the chest, abdomen, and pelvis evaluated patients for distant disease. Although the modality of local staging varied before 2014, lymph nodes, in general, were evaluated in terms of overall size, border irregularity, signal intensity heterogeneity, and shape.[10] Patients were excluded if they had recurrent or metastatic disease at presentation, had previous rectal surgery or local resection, did not undergo neoadjuvant treatment, or were medically unfit for resection at the time of diagnosis. This study was approved by the Washington University Institutional Review Board.

Treatment Regimens

Cohorts were assembled on the basis of the neoadjuvant treatment regimen received (Fig. 1). Chemoradiation involved 45 to 55 Gy of pelvic radiation delivered over 25 to 28 consecutive fractions with a concurrent fluoropyrimidine-equivalent radiosensitizer. Radiation was delivered with 3-dimensional conformal radiotherapy or intensity-modulated radiotherapy. Standard dosing of 50.4 Gy was delivered in most cases, although select boosting of extramesorectal nodes or bulky tumors resulted in cumulative doses up to 55 Gy. After an approximate 1-month recovery period, patients underwent standard total mesorectal excision (TME).[11] Adjuvant chemotherapy with a fluoropyrimidine and oxaliplatin was administered at the discretion of the treating medical oncologist.

The SC-TNT regimen was composed of hypofractionated pelvic radiation followed by consolidation chemotherapy. Radiation was delivered in 5 consecutive fractions of 5 Gy for a total dose of 25 Gy.[5] In cases of lymphadenopathy beyond the predicted resection margin, the dose was boosted to 7 Gy per fraction (total dose of 35 Gy). After 2 to 4 weeks of postradiation recovery, patients received between 2 and 6 months of platinum-based consolidation chemotherapy, most commonly mFOLFOX6. The duration of neoadjuvant chemotherapy varied over the study period because of several factors. Initial testing of the SC-TNT regimen for safety was performed with 2 months of preoperative chemotherapy and was largely applied to patients with bulky nodal disease. After 2012, more chemotherapy was added to the neoadjuvant course, eventually evolving into the current standard of 8 cycles. Chemotherapy dosing also varied by individual patient factors and treating oncologist practice patterns. Adjuvant chemotherapy administration was left to the discretion of the treating medical oncologist and varied by neoadjuvant dosing, tumor characteristics on pathologic evaluation, and oncologist treatment practices.

In the SC-TNT cohort, definitive nonoperative management was utilized selectively. Patients without evidence of residual disease on clinical, endoscopic, and radiographic restaging after completion of SC-TNT were eligible for "watch and wait."[12] Surveillance, consisting of quarterly clinical examinations, endoscopy, and pelvic MRIs, was

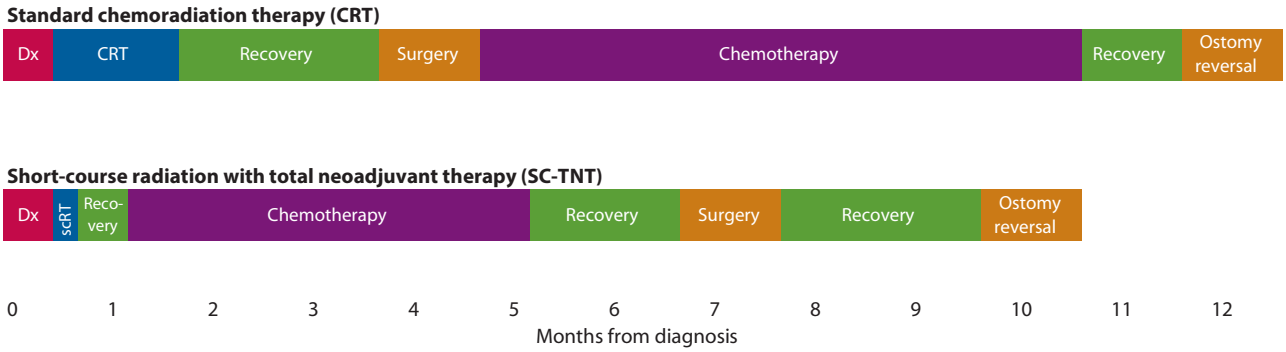

FIGURE 1. Timelines demonstrating standard treatment course for patients undergoing neoadjuvant treatment for locally advanced rectal cancer with either chemoradiation therapy or short-course radiation with total neoadjuvant therapy. Dx = diagnosis; scRT = short-course radiation therapy.

used to monitor clinical responders for regrowth for the first 2 years after treatment conclusion. Thereafter, examination frequencies were gradually reduced.[13]

Neoadjuvant regimen selection depended on the location of therapy administration. Patients receiving treatment at outside facilities throughout the study period almost exclusively received CRT. At our institution before 2016, short-course radiation was the modality of choice except in select ultra-low tumors, which intermittently received CRT at the discretion of the treating radiation oncologist. During the same time period, neoadjuvant consolidation chemotherapy was predominantly administered to tumors with concerning features such as positive circumferential resection margin or significant nodal disease, whereas patients with favorable clinical staging typically received only radiation followed by immediate surgery. Beginning in 2016, however, SC-TNT became the institutional standard therapy for all locally advanced rectal cancers treated within our institution.

Outcomes

The primary outcomes are tumor downstaging and progression-free survival. Downstaging was assessed by the rate of complete response (CR) and the rate of achieving a Neoadjuvant Rectal (NAR) score below 8 ("low").[14] When resected, patients were considered to achieve CR if the pathologic specimen was devoid of viable tumor cells (pathologic complete response). For those nonoperatively managed, absence of tumor regrowth or distant recurrence after 12 months of active surveillance was considered a CR.[1] The NAR score is a composite short-term end point designed to measure tumor response to neoadjuvant rectal cancer therapy; a "low" score (<8) has been associated with significantly improved survival in large rectal cancer trials.[14] The NAR score was calculated using clinical T, pathologic T, and pathologic N stages for each cancer (Supplementary Equation 1 at http://links.lww.com/DCR/B726); patients who did not undergo TME and experienced a durable CR were assumed to have pT = 0, pN = 0 for NAR calculation purposes.[14] Progression-free survival was defined as the time from cancer diagnosis to metastasis, local recurrence, distant recurrence, or death from any cause; patients who experienced none of these events were censored at the last recorded follow-up visit. Progression-free survival was chosen as the primary long-term oncologic outcome end point because duration, order, and modalities of therapy varied highly between cohorts.

Secondary outcomes included recurrence rates, treatment-specific characteristics including time to treatment initiation and surgery, sphincter-preservation rates, trimodal therapy completion rate, and cumulative time with a temporary ostomy. Analysis of trimodal treatment completion, defined as completion of intended radiotherapy, 3 months of oxaliplatin-containing chemotherapy, or any chemotherapy in the setting of a CR, and surgery (except in the setting of nonoperative management), was limited to patients with nonmissing chemotherapy data.

Statistical Analysis

Differences in cohort demographics, downstaging, recurrence, treatment characteristics, and sphincter preservation were analyzed with univariate χ^2 or Kruskal-Wallis tests. Disease-free survival analysis was performed by the Kaplan-Meier product-limit method with a log-rank test for statistical difference. Multivariable logistic regression analysis of CR was performed to identify adjusted associations between clinical variables and the primary end point. A level of significance where $p < 0.05$ was chosen a priori for all hypothesis testing. All analyses were performed with SAS version 9.4 (SAS Institute, Cary, NC).

RESULTS

A total of 413 eligible patients were treated with CRT (226) or SC-TNT (187) before TME or definitive nonoperative management (Table 1). Although both cohorts included similar age, sex, and clinical T-stage characteristics, SC-TNT recipients were more likely to have advanced nodal disease (cN2) (39.0% vs 16.8%; $p < 0.01$) but less likely to have distal tumors (34.2% vs 47.3%; $p < 0.01$). Treatment selection was also unevenly distributed over time; whereas both regimens were used evenly from 2009 to 2012, CRT was clearly favored in the middle 3 years before the institutional shift to SC-TNT in 2016. Accordingly, follow-up time among both cohorts was widely distributed with interquartile ranges varying from 1.5 to 5 years ($p = 0.12$).

Tumor Downstaging and Sphincter Preservation

Short-course total neoadjuvant therapy was significantly associated with higher tumor downstaging. Complete response rates were over 50% higher in the SC-TNT cohort than in the CRT group (26.2% vs 17.3%; $p = 0.03$; Table 2). Similarly, "low" NAR scores were significantly more common among SC-TNT recipients (40.1% vs 25.7%; $p < 0.01$). Short-course total neoadjuvant therapy (OR, 2.23; $p < 0.01$) remained significantly associated with CR after adjusting for cohort-level differences in multiple clinical variables (Supplementary Table 1 at http://links.lww.com/DCR/B727). Other significant associations included age over 75 years (OR, 3.07; $p = 0.02$) and T2 clinical stage (OR, 5.12; $p < 0.01$). Of note, the duration of time between radiation completion and surgery and the dose of neoadjuvant chemotherapy were not independently associated with CR on univariate analysis and were not included in the multivariable regression because of significant collinearity with the neoadjuvant treatment regimen.

TABLE 1. Study population demographic characteristics (%)

	Neoadjuvant regimen		
Variable	*CRT (n = 226)*	*SC-TNT (n = 187)*	*p value*
Age, y, n (%)			
<50	44 (19.4)	44 (23.5)	0.48
50–75	160 (70.8)	124 (66.3)	
>75	22 (9.7)	19 (10.2)	
Sex, n (%)			
Male	151 (66.8)	115 (61.5)	0.26
Female	75 (33.2)	72 (38.5)	
Year of enrollment, n (%)			
2009–2012	72 (31.9)	69 (36.8)	<0.01
2013–2015	118 (52.2)	14 (7.5)	
2016–2018	36 (15.9)	104 (55.6)	
Clinical T stage, n (%)			
T1	1 (0.4)	1 (0.5)	0.76
T2	16 (7.1)	15 (8.0)	
T3	175 (77.4)	142 (75.9)	
T4	29 (12.9)	26 (13.9)	
Missing	5 (2.2)	3 (1.6)	
Clinical N stage, n (%)			
N0	70 (31.0)	40 (21.4)	<0.01
N1	117 (51.8)	74 (39.6)	
N2	38 (16.8)	73 (39.0)	
Missing	1 (0.4)	0 (0.0)	
Clinical CRM status, n (%)			
Negative	75 (33.2)	76 (40.6)	<0.01
Close (within 2 mm)	6 (2.7)	18 (9.6)	
Positive	41 (18.1)	44 (24.1)	
Missing	104 (46.0)	49 (26.2)	
Modality for clinical staging, n (%)			
ERUS	85 (37.6)	41 (21.9)	<0.01
MRI	126 (55.8)	136 (72.7)	
MRI and ERUS	1 (0.4)	4 (2.1)	
Biopsy	3 (1.3)	0 (0.0)	
Missing	11 (4.9)	6 (3.2)	
Tumor height			
Median, cm (IQR)	5 (3–8)	7 (4–10)	0.04
Low (<5 cm), n (%)	107 (47.3)	64 (34.2)	<0.01
Mid (5–10 cm), n (%)	75 (33.2)	103 (55.1)	
High (>10 cm), n (%)	27 (12.0)	14 (7.5)	
Missing, n (%)	17 (7.5)	6 (3.2)	
Oncologic follow-up, mo			
Median (IQR)	41.6 (19.2–62.6)	28.3 (18.9–61.4)	0.12

CRM = circumferential resection margin; CRT = chemoradiation therapy; ERUS = endorectal ultrasound; IQR = interquartile range for variables described by median values; SC-TNT = short-course radiation with total neoadjuvant therapy.

In the overall study population, there was a positive association between SC-TNT and sphincter preservation (73.0% vs 60.6%; $p < 0.01$; Table 2). For patients with tumors smaller than 5 cm, the sphincter-preservation rates were similar between treatment groups (33.3% SC-TNT vs 31.8% CRT; $p = 0.83$). However, among patients who underwent sphincter-preserving resection with temporary diversion, SC-TNT was associated with significantly shorter duration of diversion (4.8 vs 7.0 months; $p < 0.01$).

Progression-Free Survival and Recurrence

Overall and site-specific recurrence patterns did not significantly vary between cohorts (Table 2); 15.6% of patients receiving SC-TNT experienced a recurrence compared with 17.4% of CRT recipients over the follow-up period ($p = 0.64$). Both neoadjuvant regimens achieved pelvic recurrence rates less than 5%, but distant recurrences were higher in both cohorts (10.7% SC-TNT vs 13.3% CRT; $p = 0.42$). Specific 2-year disease-free survival was also similar (88.2% SC-TNT (95% CI, 82.9–93.5) vs 85.6% CRT (95% CI, 80.5–90.7)), and there was no significant difference between cohorts on Kaplan-Meier analysis (log rank $p = 0.95$; Fig. 2).

Treatment Delivery Characteristics

Treatment delivery varied significantly (Table 3). Short-course total neoadjuvant therapy was associated with higher trimodality treatment completion rates (88.4% vs 50.4%; $p < 0.01$) and shorter intervals from diagnosis to consolidative chemotherapy initiation (median, 1.9 months (interquartile range (IQR), 1.6–2.5) vs 6.4 months (IQR, 5.8–7.2); $p < 0.01$) compared with CRT. Although the median time to starting any therapy was similar (1.1 months (IQR, 0.8–1.6) for both SC-TNT and CRT; $p = 0.59$), SC-TNT was associated with a longer interval from diagnosis to surgery (median, 6.2 months (IQR, 5.1–7.7) vs 4.7 months (IQR, 4.1–5.2); $p < 0.01$). Overall, total treatment time from diagnosis to diverting stoma reversal was shorter in the SC-TNT cohort (median, 10.8 months (IQR, 10.0–12.3) vs 11.5 months (IQR, 10.2–13.6); $p = 0.02$).

DISCUSSION

In North America, neoadjuvant short-course pelvic radiation is infrequently prescribed for locally advanced rectal cancer.[15,16] Despite data from Australasia[17] and Europe,[4,18] critics argue that condensed dosing risks toxicity, long-term bowel complications, and poorer oncologic outcomes compared with CRT.[8,19,20] When incorporated into a "total neoadjuvant" approach, however, we found that short-course radiation was associated with excellent oncologic outcomes, improved rates of trimodal therapy completion, and reduced burden of stoma frequency and duration.

Most importantly, SC-TNT was associated with significantly more tumor downstaging, particularly complete responses, than CRT. More than 26% of tumors in the SC-TNT group achieved a CR compared with 17% of CRT recipients, and the odds of CR (OR 2.23) were more than 100% higher for patients undergoing SC-TNT. Short-course total neoadjuvant therapy was also associated with a significantly higher proportion of "favorable" NAR scores than CRT. Notably, these results were achieved without increased risk of perioperative complications as reported previously.[21]

TABLE 2. Outcomes (%)

	Neoadjuvant regimen		
Outcome	*CRT*	*SC–TNT*	*p value*
Sphincter preservation, n (%)			
Overall	137 (60.6)	135 (73.0)	<0.01
Low tumors	34 (31.8)	21 (33.3)	0.83
Months with temporary stoma			
Median (IQR)	7.0 (5.8–8.7)	4.8 (3.5–6.2)	<0.01
Downstaging, n (%)			
CR	39 (17.3)	49 (26.2)	0.03
Low NAR score	58 (25.7)	75 (40.1)	<0.01
Recurrence, n (%)			
Total	38 (17.4)	28 (15.6)	0.64
Local	5 (2.2)	5 (2.7)	0.76
Distant	30 (13.3)	20 (10.7)	0.42
Both	3 (1.3)	3 (1.6)	0.81

Analysis limited to patients for whom all chemotherapy details, including dates of treatment, were known.
CR = complete response; CRT = chemoradiation therapy; IQR = interquartile range for variables described by median values; NAR = Neoadjuvant Rectal Score; SC-TNT = short-course radiation with total neoadjuvant therapy.

Similar associations between tumor downstaging and "total neoadjuvant" regimens utilizing chemoradiation have been previously reported. Cercek et al[1] found that higher rates of both pathologic complete response (pCR) and successful nonoperative management were significantly associated with induction chemotherapy followed by chemoradiation compared with chemoradiation alone. In the Chinese randomized "FOWARC" trial, the chemoradiation-based TNT arm achieved significantly higher complete response rates (27.5%) vs standard treatment (14.0%).[22] Additionally, the multiarmed phase II TIMING study of chemoradiation plus varying amounts of consolidative chemotherapy found stepwise increases in CR rates from 25% to 38% with the addition of more chemotherapy cycles.[3]

Previous assessments of the downstaging potential of TNT regimens incorporating short-course radiotherapy, however, offer mixed conclusions. In 2016, the Polish Colorectal Study Group reported no difference in pCR among patients with large, advanced tumors (fixed cT3 or cT4) treated with either chemoradiation and concurrent oxaliplatin infusions (12%) or a TNT regimen of 5 × 5 Gy radiation followed by 3 cycles of consolidation FOLFOX (16%; $p = 0.17$).[4] There was also no reported difference in disease-free survival. However, the recently released RAPIDO trial reported drastically different findings: 5 × 5 Gy radiation followed by approximately 4 months of consolidation chemotherapy achieved significantly more pCRs (27.7%) compared with chemoradiation (13.8%; $p < 0.01$) in a population of similarly advanced cancers (cT4, cN2, or involved mesorectal fascia).[23] And, the SC-TNT arm experienced significantly fewer disease-related treatment failures compared with chemoradiation recipients (23.7% vs 30.4%; $p = 0.02$). The divergent results of these 2 large, randomized European studies may be related to the significantly higher cumulative dose of consolidation chemotherapy or longer time interval between radiation completion and resection in the RAPIDO trial. This is also consistent with the TIMING study conclusions, which showed that more chemotherapy after chemoradiation was associated with a higher yield of pCR. The SC-TNT regimen examined in this article mirrors the RAPIDO experimental protocol much more closely, perhaps explaining the similar pCR rates (26.2% vs 27.7%) between that randomized trial and the observational data reported herein.

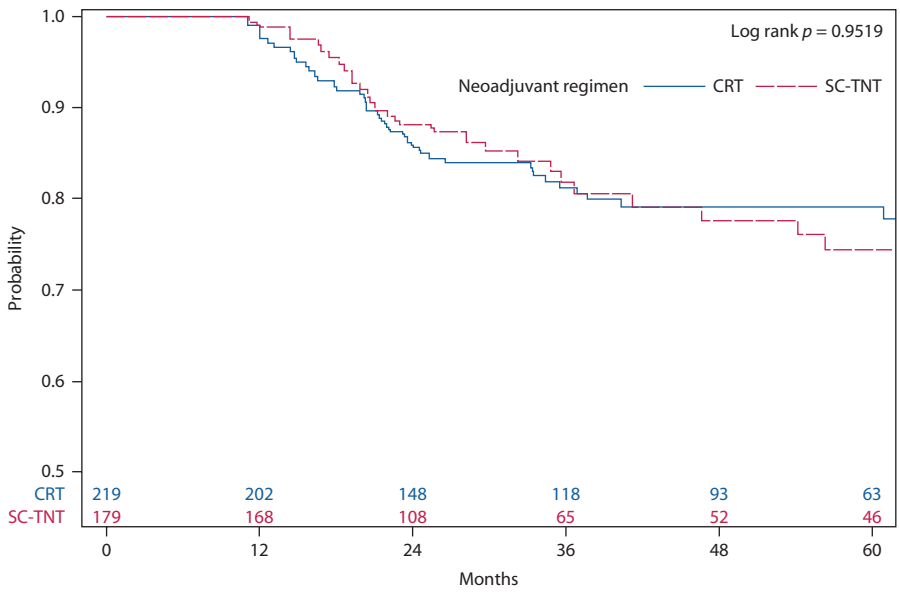

FIGURE 2. Progression-free survival curves for patients undergoing neoadjuvant treatment with either CRT (solid blue line) or SC-TNT (dashed red line). CRT = chemoradiation therapy; SC-TNT = short course radiation with total neoadjuvant therapy.

TABLE 3. Treatment characteristics by cohort (%)

Treatment variable	*CRT (n = 226)*	*SC-TNT (n = 187)*	*p value*
Radiation			
Total radiation dose received, Gy, median (IQR)	50.4 (45–50.4)	25 (25–25)	<0.01
Chemosensitizer use, n (%)			
Yes	220 (97.3)	0 (0.0)	
No	6 (2.7)	187 (100.0)	<0.01
Months from diagnosis to initiation, median (IQR)	1.1 (0.8–1.6)	1.1 (0.8–1.6)	0.59
Chemotherapy[a]			
Months from diagnosis to initiation, median (IQR)	6.4 (5.8–7.2)	1.9 (1.6–2.5)	<0.01
Neoadjuvant consolidation chemotherapy cycles			
Median (IQR)	0 (0–0)	6 (4–8)	<0.01
None, n (%)	143 (100.0)	0 (0)	<0.01
1–5, n (%)	0 (0)	54 (37.0)	
6–12, n (%)	0 (0)	92 (63.0)	
Adjuvant consolidation chemotherapy, n (%)			
Yes	186 (82.3)	107 (60.1)	<0.01
No	39 (17.3)	59 (33.1)	
Missing	1 (0.4)	12 (6.7)	
Total consolidation chemotherapy cycles			
Median (IQR)	6 (0–8)	9 (7–12)	<0.01
<6, n (%)	71 (49.6)	17 (11.6)	<0.01
≥6, n (%)	72 (50.4)	129 (88.4)	
Chemotherapy dose reduction, n (%)			
Yes	50 (22.1)	69 (36.7)	<0.01
No	176 (77.9)	118 (63.1)	
Surgery[b]			
Procedure type, n (%)			
LAR	137 (59.6)	130 (69.5)	<0.01
APR	89 (38.7)	48 (25.7)	
Definitive NOM	0 (0.0)	9 (4.8)	
Proctectomy technique, n (%)			
Open	109 (48.3)	96 (53.9)	0.20
Minimally invasive	116 (51.3)	79 (44.4)	
Missing	1 (0.4)	3 (1.7)	
Months from diagnosis to TME, median (IQR)	4.7 (4.1–5.2)	6.2 (5.1–7.7)	<0.01
Weeks from radiation completion to TME			
Median (IQR)	9 (7.9–10.6)	20 (16.5–25)	<0.01
<8, n (%)	56 (24.8)	3 (1.6)	<0.01
8–16, n (%)	152 (67.3)	31 (17.4)	
>16, n (%)	7 (3.1)	137 (77.0)	
Missing or no resection, n (%)	11 (4.8)	7 (4.0)	
Margin status, n (%)			<0.01
Negative	213 (94.3)	168 (94.4)	
Positive	13 (5.8)	3 (1.7)	
Missing or no resection	0 (0.0)	7 (3.9)	
Months from diagnosis to temporary stoma reversal[c]			
Median (IQR)	11.5 (10.2–13.6)	10.8 (10–12.3)	0.02

APR = abdominoperineal resection; CRT = chemoradiation therapy; Gy = Gray; IQR = interquartile range for variables described by median values; LAR = low anterior resection;
NOM = nonoperative management; SC-TNT = short-course radiation with total neoadjuvant therapy; TME = total mesorectal excision.
[a] Analysis limited to patients for whom all chemotherapy details, including dates of treatment, were known.
[b] Analysis excludes NOM recipients except where explicitly noted.
[c] Only LAR recipients never nonoperatively managed included.

To date, no comparison of tumor downstaging between TNT regimens utilizing short-course radiation versus chemoradiation (CRT-TNT) has been performed. Short-course 5 × 5 Gy has a biological effective dose of approximately 37.5 Gy (for α/β ratio of 10), whereas 5 × 6 Gy may more closely approximate standard 50.4 Gy in 28 fractions. Although comparisons across trials suggest that CRT-TNT may increase downstaging, studies performing direct comparisons are needed to evaluate optimal dosing.

The relationship between TNT regimens and survival, however, is more complex. In our series, SC-TNT showed no significant association with recurrence rate or progression-free survival despite earlier initiation of chemotherapy and higher therapy completion rates. The lack of observed survival benefit in patients receiving SC-TNT

in our data may be related to the uneven distribution of follow-up time between cohorts. However, the same trend was noted in other studies; the phase II Spanish GCR-3 trial also reported no difference in 5-year disease-free survival between TNT recipients and those receiving chemoradiation and adjuvant chemotherapy.[24] Long-term follow-up from the FOWARC trial also found no difference in 3-year disease-free survival and overall survival between chemoradiation or TNT groups.[25] Although the Polish Colorectal Study Group reported initially increased overall survival in the short-course arm (73% vs 65%; $p = 0.04$),[4] long-term follow-up in this cohort found no survival difference at 7 years.[26] Yet survival analysis from the Timing of Rectal Cancer Response to Chemoradiation Study Consortium found a positive association between neoadjuvant consolidative chemotherapy and disease-free survival that was not sensitive to dose of chemotherapy.[27] Because treatment completion, in general, is much higher among those receiving chemotherapy neoadjuvantly,[1] the conflicting conclusions regarding survival among TNT recipients are surprising and require further study.

Treatment completion and tolerance also varied between cohorts. Short-course total neoadjuvant therapy recipients received 80% fewer radiation treatments and initiated multiagent chemotherapy 4.5 months sooner than patients receiving chemoradiation. Eighty-eight percent of patients receiving SC-TNT completed trimodal therapy, a surrogate marker of treatment tolerance, compared with 50% of those treated with chemoradiation and adjuvant therapy. Short-course total neoadjuvant therapy was associated with significantly less time with diverting ostomies. Finally, the cumulative treatment course was shorter in the SC-TNT cohort (10.8 vs 11.5 months); whether this difference is attributable to shortened radiation duration or other factors remains untested. Overall, SC-TNT was associated with fewer treatment visits, marginally shorter treatment courses, and higher treatment completion compared with CRT.

In summary, SC-TNT achieves excellent oncologic outcomes while meeting many goals of current oncologic therapy. Surgery is performed after completion of all chemotherapy and even avoided in select cases. The cumulative radiation dose is reduced, and the time patients bear a temporary stoma is significantly shortened. Most importantly, the oncologic outcomes are, at minimum, equivalent with traditional therapy. These findings mirror recently released randomized data from the OPRA[28] and RAPIDO trials,[23] further supporting the utilization of delayed surgery and short-course TNT regimens in North America. Short-course total neoadjuvant therapy is an ideal regimen for rectal cancer treatment in the contemporary era.

Limitations

The results and conclusions of this study must be considered within the context of several limitations. First, the 2 cohorts differed significantly in location of treatment because many patients undergoing CRT received their initial neoadjuvant therapy from referring oncologists. Although all patients underwent resection and surveillance at our medical center, the difference in location of neoadjuvant treatment could not be controlled in this study and may account for some of the observed differences in outcomes between cohorts. Second, criteria for utilizing CRT at Washington University before 2016 were not standardized; therefore, treatment selection may have biased the results of this analysis. Cohort imbalance in tumor height and nodal disease burden may represent such bias, in particular, because SC-TNT was preferentially used in patients with cN2 disease and higher tumors before institutional standardization. Third, cumulative follow-up time is imbalanced between cohorts because a higher proportion of patients received CRT early in the study period (before SC-TNT was adopted). Therefore, CRT recipients have accumulated more follow-up time and bear an increased risk of recurrence (Supplementary Figure 1 http://links.lww.com/DCR/B725). Finally, the retrospective nature of this analysis precludes evaluation of any causative relationship between the neoadjuvant regimen and the outcomes of interest or the independent effect of clinical variables such as radiation course, time from radiation to surgery, or amount of neoadjuvant chemotherapy. Also, the retrospective design precluded analysis of some variables inconsistently collected across the study period, including the total number of rectal cancers treated during the study period, the percentage of cancers required emergent diversion in setting of obstruction, T-stage subclassification, and MRI-detected extramural vascular invasion status. Longer follow-up and prospective studies are needed to determine whether such biases alter the material conclusions of this analysis.

CONCLUSION

Compared with standard CRT, SC-TNT was associated with higher rates of tumor downstaging, improved treatment completion, and fewer months with temporary stomas among patients with locally advanced rectal cancer. There was no difference in recurrence or progression-free survival between regimens despite earlier chemotherapy administration and higher therapy completion rates in the SC-TNT group.

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