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REVIEW ARTICLE – COLORECTAL CANCER

Total Neoadjuvant Therapy in Locally Advanced Rectal Cancer: A Systematic Review and Metaanalysis of Oncological and Operative Outcomes

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ABSTRACT

Background. Total neoadjuvant therapy in rectal cancer refers to the administration of chemoradiotherapy plus chemotherapy before surgery. Recent studies have shown improved pathological complete response and disease-free survival with this approach. However, survival benefits remain unproven. Our objective is to present a metaanalysis of oncological outcomes of total neoadjuvant therapy in locally advanced rectal cancer.

Patients and Methods. A comprehensive search was performed on PubMed, Medline, and Google Scholars. Studies comparing total neoadjuvant therapy with standard neoadjuvant chemoradiotherapy were included. Data extracted from the individual studies were pooled and a metaanalysis performed. The outcomes of interest are the rate of complete pathological response, nodal response, resection margin, anal preservation, anastomotic leak, local recurrence, distant recurrence, disease-free survival, and overall survival.

Results. There were 15 comparative studies with 2437 patients in the neoadjuvant chemoradiotherapy group and 2284 in the total neoadjuvant therapy group. The pooled complete pathological response was 22.3% in the total neoadjuvant therapy group, compared with 14.2% in the standard neoadjuvant chemoradiotherapy group ($p < 0.001$). Even though there was no difference in local recurrence rate, there was a significantly lower rate of distant recurrence (OR 0.81, $p = 0.02$), and better 3-year disease-free survival (70.6% vs. 65.3%, respectively, $p < 0.001$) and overall survival (84.9% vs. 82.3%, respectively, $p = 0.006$), favoring the total neoadjuvant therapy group. Due to significant heterogeneity in the study protocols, there remains uncertainty on the ideal chemotherapy/radiotherapy sequence.

Conclusions. This study provides supporting evidence on the favorable immediate and intermediate oncological outcomes with the use of total neoadjuvant therapy for locally advanced rectal cancer.

Joseph C. Kong and Mikael Soucisse are co-first authors and have contributed equally to this study.

Local recurrence in rectal cancer has significantly improved following the inception and standardization of total mesorectal excision (TME) surgery,[1] as well as increased uptake of either preoperative long-course chemoradiotherapy (LCCRT) or short-course radiotherapy (SRT).[2,3] Despite this multidisciplinary approach to care including the use of adjuvant chemotherapy, the risk of distant relapse remains relatively static and is the leading

cause of mortality in this patient population.[4] Furthermore, there have been several randomized control trials (RCTs) and one metaanalysis showing a lack of benefit for advocating adjuvant chemotherapy in patients who had received neoadjuvant chemoradiotherapy (nCRT) for rectal cancer.[5–8] Nevertheless, most national guidelines include this as a standard of care,[9,10] perhaps an extrapolation from trial of adjuvant chemotherapy in colon cancer.

Studies aimed at optimizing this paradigm have demonstrated a potential advantage in delaying surgery to maximize the impact of neoadjuvant therapies. A 10- to 12-week wait from the completion of neoadjuvant radiotherapy to surgery, for example, has been shown to decrease local recurrence but with heterogenous effects on postoperative complications and TME quality.[11–14] This increased time period has provided an opportunity to trial additional preoperative chemotherapy. Delivering systemic chemotherapy in the neoadjuvant setting, either before or after radiotherapy for rectal cancer has been termed total neoadjuvant therapy (TNT). The value of this approach has been studied, and early results have demonstrated high rates of completion and tolerability, complete pathological response (pCR) between 20 and 30%, sphincter sparing surgery, and R0 resection.[15–17] This approach attempts to overcome the decreased compliance of adjuvant chemotherapy for rectal cancer compared with colon cancer, which is hypothesized to be one of the reasons why a survival benefit has never been demonstrated.

Other possible benefits of delivering systemic chemotherapy early in the neoadjuvant setting in patients with locally advanced rectal cancer include the early prevention or eradication of micrometastases, minimizing the length of time patients need an ileostomy[18] and facilitating the surgical resection by decreasing the bulk of the tumor and nodes. In high-risk patients, intensified neoadjuvant combination chemotherapy has the added benefit of assessing the tumor biology and selecting the best approach for a given patient. In case of marked progression on therapy, a resection might be futile, while a complete clinical response might allow an organ preservation approach in selected patients.

A previous metaanalysis by Petrelli et al. on the subject of TNT is limited by mainly nonrandomized studies.[19] Since this last metaanalysis, there have been five additional reported studies, of which three were RCTs.[20–24] With results now available from these additional RCTs, we seek to reassess the potential benefits of the TNT approach in locally advanced rectal cancer. The objective of our present metaanalysis is to evaluate the oncological outcomes of patients with locally advanced rectal cancer, comparing TNT versus standard nCRT or SRT before surgery, specifically the differences in tumor downstaging, resection margins, local recurrence, distant recurrence, and postoperative complications.

PATIENTS AND METHODS

A systematic search was performed according to the Preferred Reporting Items for Systematic Reviews and Metaanalysis (PRISMA) guidelines. The last date of the search was 7 December 2020 from PubMed, Ovid Medline, and Google Scholars. The following Medical Subject Headings (MeSH) terms were used; "neoadjuvant therapy" OR "total neoadjuvant treatment" OR "neoadjuvant" OR "chemotherapy" OR "chemoradiotherapy" OR "radiotherapy" AND "rectal cancer" OR "rectal adenocarcinoma." A further search was performed in clinicaltrials.gov using the search terms "neoadjuvant therapy" and "rectal cancer." A bibliographic search was also performed to identify additional studies from the included studies. Initially, all titles were screened, and abstracts reviewed if there were any uncertainties of study inclusion. Finally, all potential studies for inclusion were retrieved, and full text reviewed. From the clinicaltrials.gov, conference abstracts were retrieved if results had not been published in a peer-reviewed journal. To maintain a high standard in this metaanalysis, conference abstracts were not included in the final analysis.

Therefore, the inclusion criteria were as follow: (a) adult participants ≥ 18 years, (b) published studies comparing standard neoadjuvant therapy (short-course radiotherapy or long-course chemoradiotherapy) versus total neoadjuvant therapy, (c) locally advanced rectal cancer (cT3–4 and/or N+), and (d) rectal cancers measured ≤ 12 cm. The following studies were excluded: (a) if there was an addition of a biologic agent such as anti-epidermal growth factor or anti-vascular endothelial growth factor, (b) studies investigating nonoperative rectal preservation or "watch and wait" strategy, and (c) letters to editor, systematic reviews, and conference abstracts.

Two reviewers (J.C.K. and M.S.) collected the data independently, with any discrepancy (less than 5%) resolved by consensus with S.K.W. There were nine outcomes of interest: the rate of complete pathological response (pCR, defined as T0N0), pN0, R0, anal preservation, anastomotic leak, local recurrence, distant recurrence, disease-free survival (DFS), and overall survival (OS). Data collection includes author, year of publication, study design, neoadjuvant short-course or long-course regimen, total neoadjuvant therapy regimen, patient selection, interval time to surgery, follow-up, and outcome measures.

Interval time to surgery and follow-up timelines were collected as median and categorical data reported as

percentage converted to absolute numbers, including OS and DFS. The interval time to surgery was defined as time from last treatment delivered (either chemoradiation or consolidation chemotherapy) to surgery. Induction total neoadjuvant therapy was defined as chemotherapy regimen delivered before radiotherapy, and consolidation total neoadjuvant therapy was defined as chemotherapy regimen delivered after radiotherapy. For studies that did not report the percentage for DFS and OS, an estimated percentage was derived from their respective Kaplan–Meier curves. In data that reported zero events, this was replaced as 0.5 to allow for the computation of statistical calculation. Outcome measures with categorical data such as pCR, pN0, R0, anal preservation, anastomotic leak, local and distance recurrence, for each study their odds ratio (OR) and associated 95% confidence interval (CI) were calculated. As for DFS and OS, the absolute numbers were converted to relative risk and associated 95% CI. Due to potential study heterogeneity, pooled relative risk (RR) was performed using the random-effects (RE) model, whereas pooled OR was performed using the Cochran–Mantel–Haenszel test.

I^2 statistics were used to assess for interstudy heterogeneity and can be interpreted as 0–30% for minimal, 30–60% moderate, 60–90% substantial, and 90–100% considerable heterogeneity. Egger's test was performed to assess for publication bias. The Newcastle–Ottawa scale was used to assess each nonrandomized study's quality, and a score of ≥ 6 is of good quality.[23] The Jadad scale was used to assess the quality of randomized controlled trials. Trials with a Jadad score of > 3 were included. A p value of < 0.05 was considered significant. All data analysis was performed in R Studio Team (2015). RStudio: Integrated Development for R Studio, Inc., Boston, MA, and using the metaphor package for metaanalysis.[25]

RESULTS

Literature Search Results

After eliminating duplicates and screening abstracts, 48 articles were assessed for eligibility. After exclusions, 15 comparative studies were included in the final analysis. The full detail of the inclusions process and PRISMA flow chart can be found as eFig. 1 in the online supplement. We identified five retrospective observational studies,[18,22,23,26,27] three prospective nonrandomized studies,[28–30] and seven randomized controlled trials.[16,21,31–36] Table 1 summarizes the characteristics of the included studies. In total, there were 2437 patients treated by standard NCRT, and 2284 patients received TNT. Nine studies used induction TNT, whereas six studies were consolidation TNT. A total of 12 studies used long-course

chemoradiotherapy (approximately 50 Gy) in both nCRT and TNT groups. One study used short-course radiotherapy (SRT; 25 Gy in five fractions) in the control and experimental groups.[29] Two studies, including the recently published RAPIDO trial, used SRT in combination with FOLFOX or CAPOX in their TNT group, while the patients in the control group received 50.4 Gy LCCRT.[31,35] The mean Jadad score was 3.375 for randomized studies, and the mean Newcastle–Ottawa scale score for nonrandomized studies was 6.875. Overall, 11 studies reported their median follow-up, which ranged from 26 to 72.6 months. The interval time to surgery was quite variable in different studies, ranging from 4 to 25 weeks, depending on the number of cycles of chemotherapy in the TNT group and the waiting time after radiation was completed.

Metaanalyses

Complete Pathological Response and Nodal Downstaging A total of 14 studies reported on pCR, favoring the use of TNT, which showed an increase in odds of pCR by 51% (pooled OR 1.51, 95% CI 1.29–1.78, $p < 0.001$, $I^2 = 40.1\%$; Cochran–Mantel–Haenszel test; Fig. 1). The pooled rate of pCR in the TNT group was 20.5% (15.5–27.5%) versus 14% (12.2–22.2%) in the nCRT group. Ten studies had data on nodal downstaging. Patients who received TNT were less likely to have residual nodal disease on final pathology (pooled OR 0.87, 95% CI 0.73–1.03, $p = 0.122$, $I^2 = 67.7\%$; eFig. 2), although not statistically significant.

Resection Margins Resection margin status was available in 12 studies for analysis. The patients who received TNT were 34% less likely to have positive surgical margins (0.66, 95% CI 0.51, 0.87, $p = 0.003$, $I^2 = 46.1\%$; eFig. 3)

Anastomotic Leak Anastomotic leak was the only postoperative morbidity consistently reported through studies suitable for metaanalysis. Six studies reported on the rate of anastomotic leak for comparison. No difference was found in the two groups (pooled OR 0.91, 95% CI 0.53–1.55, $I^2 = 0\%$; eFig. 4). The pooled anastomotic leak rate was 8.4% and 8.7% in the TNT and nCRT groups.

Anal Preservation Data from seven comparative studies were available for analysis on the ability to perform an anal preserving resection after neoadjuvant treatment. Patients in the TNT group were significantly less likely to need an abdominoperineal resection than the nCRT group (OR 0.77, 95% CI 0.62–0.97, $p = 0.031$, $I^2 = 58.6\%$; eFig. 5)

TABLE 1 Study, treatment sequence, and tumor and patient characteristics

Author	Year	Study design	Neoadjuvant CRT	TNT	Treatment sequence	Patient selection	No. patients NCRT	No. patients TNT	Follow-up	ITS weeks (median)	NOS or Jadad
Bahadoer et al. *	2020	Phase III, multicentre RCT (RAPIDO)	Cap + 50.4 Gy + adjuvant CAPOX/FOLFOX	25 Gy + CAPOX/FOLFOX4	C	T4, N2, EMVI, threatened CRM, enlarged LPLN	450	462	NR	6-8 ‡€ 2-4 æ€	4 Jadad
Deng et al.	2019	Phase III, multicentre RCT	5-FU + leucovorin + 50.4 Gy	mFOLFOX6 + 50.4 Gy	I	cT3-4, N+	141	149	45.2 (1-83)	NR	3 Jadad
Liang et al.	2019	ROS	Cap/CAPOX/FOLFOX + 50.4 Gy + adjuvant Cap/CAPOX/FOLFOX	Cap/CAPOX/FOLFOX + 50.4 Gy	I	cT3-4, N+	80	76	31 (4-84)	7.4 ‡ 8.7 æ	6 NOS
Quezada-Diaz et al.	2019	ROS	Cap/5-FU + 50.4 Gy	mFOLFOX6/CAPOX/ FLOX + 50.4 Gy	I	cT3-4, N+	34	98	NR	NR	6 NOS
Zhu et al.	2019	ROS	50.4 Gy	NRle 1	I	cT3-4, N+	707	372	33.7	NR	7 NOS
Cercek et al.	2018	ROS	5-FU/Cap + 50.4 Gy	FOLFOX/CAPOX/FLOX + 5-FU/ Cap + 50.4 Gy	I	cT3-4, N+	296	279	40 (6-92)	NR	7 NOS
Kim et al.	2018	Phase II, multicentre RCT (KCSG C0 14-03)	Cap + 50.4 Gy	Cap + 50.4 Gy + CAPOX	C	cT3-4, N+	52	44	26 (0.8-39.4)	11 €	3 Jadad
Marco et al.	2018	Phase II, multicentre nonrandomized trial	5-FU + 50.4 Gy	5-FU + 50.4 Gy + mFOLFOX6	C	cT3-4, N+	60	65	59 (9-125)	NR	7 NOS
Markovina et al.	2017	Phase II, prospective study	5-FU + 25/50.4 Gy + adjuvant FOLFOX/ CAPOX	5-FU + 25 Gy + mFOLFOX6/CAPOX	C	cT3-4, N+	69	69	49-54	NR	7 NOS
Moore et al.	2017	Phase II, RCT	5-FU + 50.4 Gy	5-FU + 50.4 Gy + 5-FU + leucovorin	C	cT3-4, N+	24	25	NR	10 €	3 Jadad
Bujko et al.	2016	RCT	5-FU + AF + Ox + 50.4 Gy	25 Gy + FOLFOX4	C	cT3-4	254	261	35	NR	4 Jadad
Bhatti et al.	2015	ROS	Capecitabine + 50.4 Gy	Capecitabine + oxaliplatin + 50.4 Gy	I	cT3-4, N+	61	93	45 (15-72)	6-8 €	7 NOS
Fernandez-Martos et al.	2015	Phase II, multicentre RCT (GCR-3)	50.4 Gy + adjuvant CAPOX	CAPOX + 50.4 Gy	I	cT3-4	52	56	69	5-6 €	4 Jadad
Calvo et al.	2014	POS	5-FU + 50.4 Gy	FOLFOX4 + 5-FU + 50.4 Gy	I	cT3-4, N+	128	207	72.6 (4-205)	6	8 NOS
Marechal et al.	2012	Phase II RCT	5-FU + 50.4 Gy	mFOLFOX6 + 5-FU + 50.4 Gy	I	cT2-4, N+	29	28	NR	4-6 €	3 Jadad

ITS interval time to surgery is reported as last dose of chemoradiation or consolidation chemotherapy, *RAPIDO* Rectal cancer and preoperative induction therapy followed by Dedicated Operation, *KCSG* Korean Cancer Study Group, *FOWARC* Chemotherapy With or Without Radiation in Rectal Cancer, *RCT* randomized control trial, *ROS* retrospective observational study, *POS* prospective observational study, *I* induction total neoadjuvant therapy, *C* consolidation total neoadjuvant therapy, *EMVI* extramural venous invasion, *CRM* circumferential resection margin, *LPLN* lateral pelvic lymph node, *NR* not reported, *ITS* interval time to surgery. *NOS* Newcastle–Ottawa Scale

Author and Year	TNT (+)	TNT (−)	NCRT (+)	NCRT (−)	Weight		Odds Ratio [95%CI]
Bahadoer et al., 2020	120	423	57	398	19.8		1.98 [1.40, 2.79]
Deng et al., 2019	41	108	20	121	6.1		2.30 [1.27, 4.16]
Liang et al., 2019	16	60	9	71	2.8		2.10 [0.87, 5.10]
Quezada−Diaz et al., 2019	21	77	12	22	5.7		0.50 [0.21, 1.17]
Zhu et al., 2019	63	309	93	614	21.9		1.35 [0.95, 1.91]
Cercek et al., 2018	44	235	49	247	16.4		0.94 [0.61, 1.47]
Kim et al., 2018	6	38	3	49	1		2.58 [0.61, 10.99]
Marco et al., 2018	25	40	11	49	2.9		2.78 [1.22, 6.34]
Markovina et al., 2017	19	50	11	58	33		2.00 [0.87, 4.61]
Moore et al., 2017	5	20	6	18	2		0.75 [0.20, 2.88]
Bujko et al., 2016	37	224	24	230	8.6		1.58 [0.92, 2.73]
Bhatti et al., 2015	29	64	13	48	4.4		1.67 [0.79, 3.55]
Fernandez−Martos et al., 2015	8	46	7	39	2.7		0.97 [0.32, 2.91]
Marechal et al., 2012	7	21	8	21	2.4		0.88 [0.27, 2.85]
Total	441 (20.5%)	1715 (79.5%)	323 (14%)	1985 (86%)	100%		1.51 [1.29, 1.78]

Pooled Odds Ratio
Heterogeneity:I2=40.1%, p−value=0.061
Cochran−Mantel−Haenszel Test: p−value<0.001
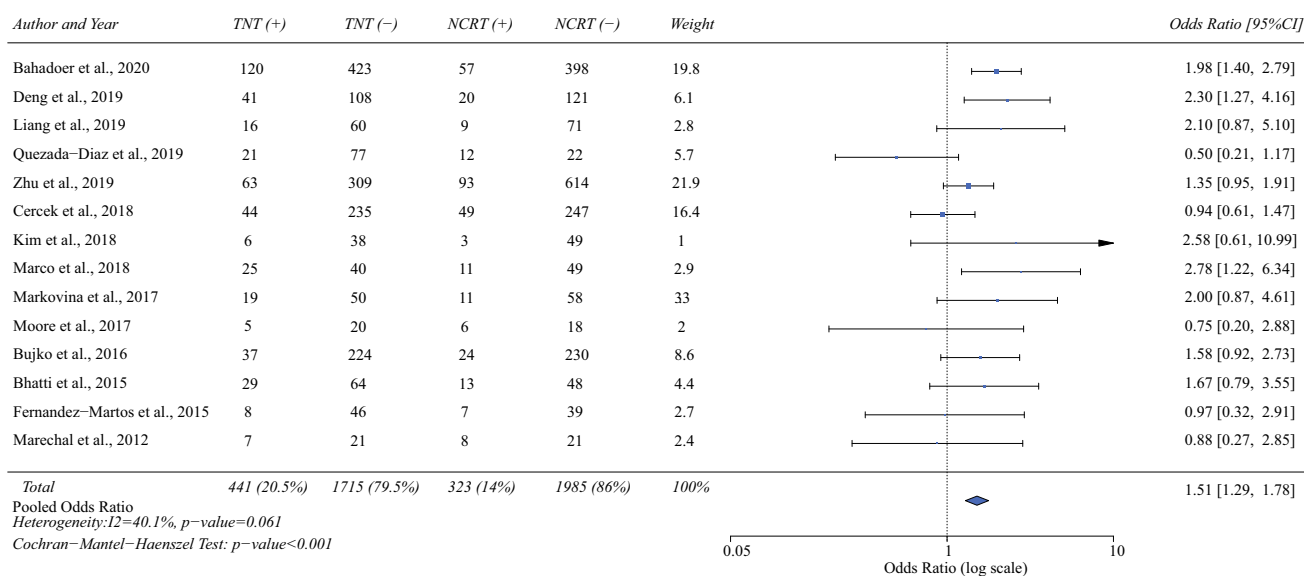
Odds Ratio (log scale): 0.05 — 1 — 10

FIG. 1 Comparing rate of complete pathological response in total neoadjuvant therapy versus standard neoadjuvant chemoradiotherapy

Local and Distant Recurrence No differences were found in local recurrences after pooling data from seven studies (OR 1.29, 95% CI 0.95–1.74, $I^2 = 42.1\%$, eFig. 6). Data on distant recurrences were available in six studies. Albeit moderate to substantial heterogeneity, patients who received TNT were 22% less likely to develop distant recurrences (OR 0.78, 95% CI 0.63–0.96, $p = 0.003$, $I^2 = 72.1\%$; Fig. 2)

Survival Outcomes Three-year DFS and OS data were available in eight studies for quantitative analysis. The TNT group patients were significantly less likely than the nCRT group to have disease recurrence at three years, 31.9% versus 26.8%, respectively (RR 0.86, 95% CI 0.77–0.96, $p < 0.007$, $I^2 = 0.96\%$; random-effect model; Fig. 3). This DFS advantage also translated in a significant advantage in 3-year OS in favor of TNT (RR 0.83, 95% CI 0.71–0.97, $p = 0.019$, $I^2 = 55.3\%$; Fig. 4). The pooled 3-year survival was 85.5% (76.3–90.2%) and 83.3% (72.5–89.1%) in the TNT and nCRT groups, respectively.

Sub-Metaanalyses

A summary of the outcomes from sub-metaanalyses comparing induction versus consolidation-type TNT can be found in Table 2.

Induction Chemotherapy-Type TNT All studies in this subgroup analysis used long-course CRT (LCCRT) either alone or after induction chemotherapy. pCR, nodal downstaging, resection margin status, and recurrence analyses were repeated while including only the studies which used induction chemotherapy as part of their TNT

protocol. After removing patients who received consolidation chemotherapy, patients in the TNT group were 28% more likely to have complete pathological response (OR 1.28, 95% CI 1.04–1.58, $p = 0.022$, $I^2 = 44.5\%$; eFig. 7), 44% less likely to have residual nodal disease at surgery (OR 0.56, 95% CI 0.41–0.77, $p < 0.001$, $I^2 = 33.5\%$; eFig. 8) and 57% less likely to have positive margins (OR 0.43, 95% CI 0.27–0.66, $p = 0.001$, $I^2 = 43.1\%$; eFig. 9). There were no differences in the rate of local recurrences and distant recurrences, as seen in eFigs. 10 and 11, respectively.

Consolidation Chemotherapy-Type TNT pCR, nodal downstaging, resection margins status, and recurrence analyses were repeated after eliminating studies that used induction chemotherapy in their TNT protocol. Of note, three of the six studies in this subgroup analysis also used SRT instead of LCCRT. Similar to induction-type TNT, patients who received consolidation-type TNT were 90% more likely to have complete pathological response (OR 1.90, 95% CI 1.48–2.45, $p < 0.001$, $I^2 = 0.00\%$; eFig. 12). Contrary to the results of the induction sequence of TNT, consolidation-type TNT failed to provide better nodal downstaging (OR 1.05, 95% CI 0.85–1.30, $p = 0.717$, $I^2 = 66.5\%$; eFig. 13) and had similar positive margins rates to standard LCCRT (OR 0.87, 95% CI 0.62–1.22, $p = 0.472$, $I^2 = 3.82\%$; eFig. 14). Interestingly, the only studies that had extractable recurrence data in the consolidation TNT subgroup were the three studies that used SRT instead of LCCRT. The pooled data of these three studies, including the recently published RAPIDO trial, demonstrated a significant 27% reduction in the odds of distant recurrence (OR 0.73, 95% CI 0.58–0.92,
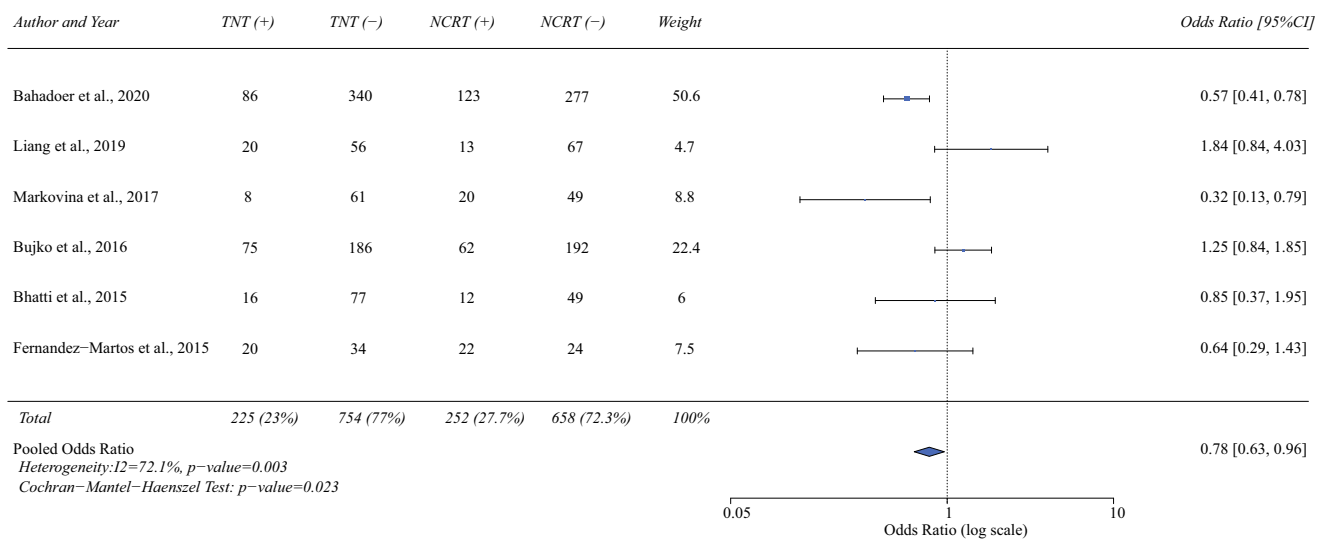
Author and Year	TNT (+)	TNT (−)	NCRT (+)	NCRT (−)	Weight		Odds Ratio [95%CI]
Bahadoer et al., 2020	86	340	123	277	50.6		0.57 [0.41, 0.78]
Liang et al., 2019	20	56	13	67	4.7		1.84 [0.84, 4.03]
Markovina et al., 2017	8	61	20	49	8.8		0.32 [0.13, 0.79]
Bujko et al., 2016	75	186	62	192	22.4		1.25 [0.84, 1.85]
Bhatti et al., 2015	16	77	12	49	6		0.85 [0.37, 1.95]
Fernandez−Martos et al., 2015	20	34	22	24	7.5		0.64 [0.29, 1.43]
Total	225 (23%)	754 (77%)	252 (27.7%)	658 (72.3%)	100%		
Pooled Odds Ratio Heterogeneity:I2=72.1%, p−value=0.003 Cochran−Mantel−Haenszel Test: p−value=0.023							0.78 [0.63, 0.96]

Odds Ratio (log scale) 0.05 1 10

FIG. 2 Comparing rate of distant recurrences in total neoadjuvant therapy versus standard neoadjuvant chemoradiotherapy

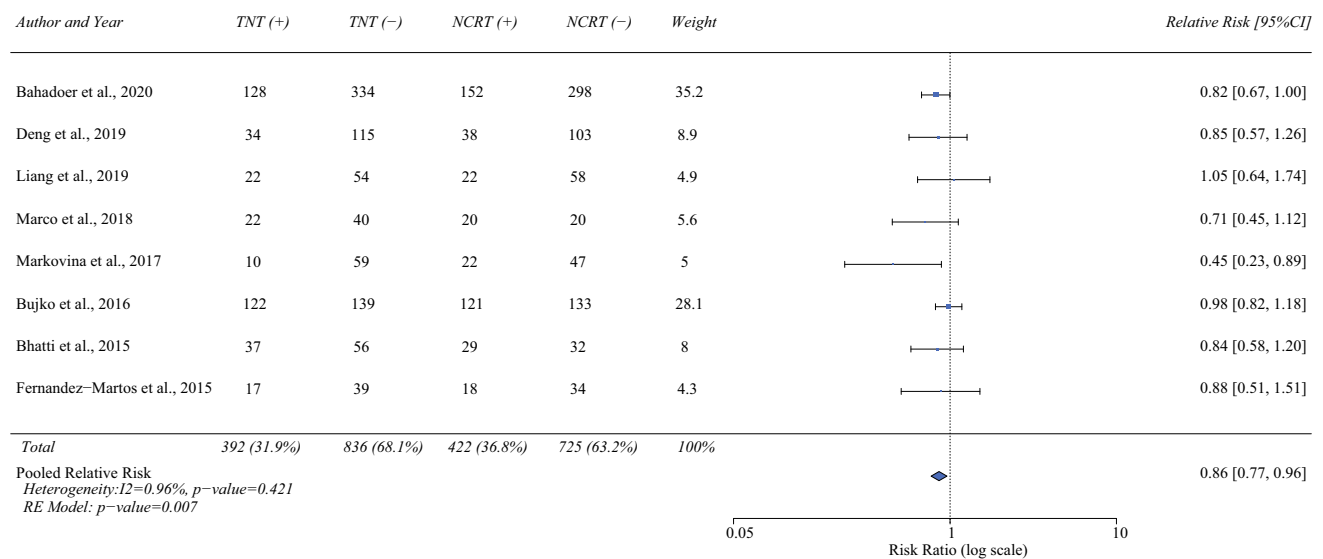| Author and Year	TNT (+)	TNT (−)	NCRT (+)	NCRT (−)	Weight		Relative Risk [95%CI]
Bahadoer et al., 2020	128	334	152	298	35.2		0.82 [0.67, 1.00]
Deng et al., 2019	34	115	38	103	8.9		0.85 [0.57, 1.26]
Liang et al., 2019	22	54	22	58	4.9		1.05 [0.64, 1.74]
Marco et al., 2018	22	40	20	20	5.6		0.71 [0.45, 1.12]
Markovina et al., 2017	10	59	22	47	5		0.45 [0.23, 0.89]
Bujko et al., 2016	122	139	121	133	28.1		0.98 [0.82, 1.18]
Bhatti et al., 2015	37	56	29	32	8		0.84 [0.58, 1.20]
Fernandez−Martos et al., 2015	17	39	18	34	4.3		0.88 [0.51, 1.51]
Total	392 (31.9%)	836 (68.1%)	422 (36.8%)	725 (63.2%)	100%		
Pooled Relative Risk Heterogeneity:I2=0.96%, p−value=0.421 RE Model: p−value=0.007							0.86 [0.77, 0.96]

Risk Ratio (log scale) 0.05 1 10

FIG. 3 Comparing 3-year disease-free survival in total neoadjuvant therapy versus standard neoadjuvant chemoradiotherapy

$p = 0.09$, $I^2 = 84.3\%$; eFig. 15), but at the cost of an 86% higher likelihood of local recurrence (OR 1.86, 95% CI 1.23–2.80, $p = 0.04$, $I^2 = 0.00\%$; Fig. 5). The pooled recurrence rate was 9.3% (6.8–13.4%) versus 5.3% (4.3–7.1%) in the consolidation TNT and non-TNT groups, respectively. Furthermore, this finding of an increased risk of local recurrence had almost no heterogeneity across all studies that use SRT for locally advanced rectal cancer.

Publication Bias An Egger's test for publication bias was performed for pCR, given the significant findings with the highest number of publications included in the pooled analysis. It did not show a significant publication bias with $p = 0.689$, as shown in eFig. 16.

DISCUSSION

The current metanalysis of 15 studies, including 7 randomized control trials, showed favorable outcomes with TNT over standard treatment strategies. An improved nodal response and complete pathological response was observed; a more favorable surgical margin status (R0 resection) was also seen, with no additional morbidity observed. While no difference in local recurrence was seen with TNT, an improved distant recurrence, 3-year DFS, and OS favoring total neoadjuvant therapy are compelling.

The rationale for a TNT strategy is to reduce a patient's risk of distant recurrence, which was demonstrated in all the pooled studies. The role of adjuvant chemotherapy in the setting of locally advanced rectal cancer treated with
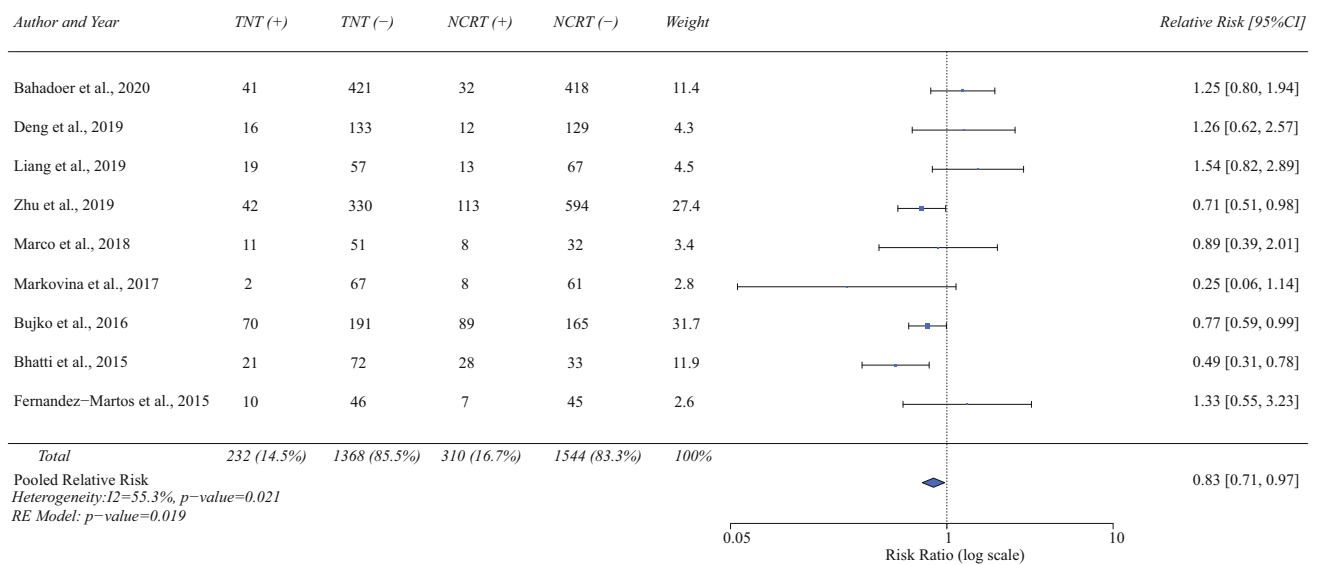
Author and Year	TNT (+)	TNT (−)	NCRT (+)	NCRT (−)	Weight		Relative Risk [95%CI]
Bahadoer et al., 2020	41	421	32	418	11.4		1.25 [0.80, 1.94]
Deng et al., 2019	16	133	12	129	4.3		1.26 [0.62, 2.57]
Liang et al., 2019	19	57	13	67	4.5		1.54 [0.82, 2.89]
Zhu et al., 2019	42	330	113	594	27.4		0.71 [0.51, 0.98]
Marco et al., 2018	11	51	8	32	3.4		0.89 [0.39, 2.01]
Markovina et al., 2017	2	67	8	61	2.8		0.25 [0.06, 1.14]
Bujko et al., 2016	70	191	89	165	31.7		0.77 [0.59, 0.99]
Bhatti et al., 2015	21	72	28	33	11.9		0.49 [0.31, 0.78]
Fernandez−Martos et al., 2015	10	46	7	45	2.6		1.33 [0.55, 3.23]
Total	232 (14.5%)	1368 (85.5%)	310 (16.7%)	1544 (83.3%)	100%		
Pooled Relative Risk							0.83 [0.71, 0.97]

Heterogeneity:I2=55.3%, p−value=0.021
RE Model: p−value=0.019

FIG. 4 Comparing 3-year overall survival in total neoadjuvant therapy versus standard neoadjuvant chemoradiotherapy

TABLE 2 Summary of study subanalyses compared with pooled analyses

Outcomes	Induction TNT	Consolidation TNT	RCT only	All studies
pCR	1.28 (1.04–1.58; $p = 0.022$)	1.90 (1.48–2.45; $p < 0.001$)	1.78 (1.48–2.26; $p < 0.001$)	1.51 (1.29–1.78; $p < 0.001$)
pN+	0.56 (0.41–0.77; $p < 0.001$)	1.05 (0.85–1.30; $p = 0.717$)	0.87 (0.72–1.06; $p = 0.176$)	0.87 (0.73–1.03; $p = 0.122$)
Positive margin	0.43 (0.27–0.66; $p = 0.001$)	0.87 (0.62–1.22; $p = 0.472$)	0.93 (0.67–1.31; $p = 0.760$)	0.66 (0.51–0.87; $p = 0.003$)
Local recurrence	0.77 (0.48–1.24; $p = 0.347$)	1.86 (1.23–2.80; $p = 0.004$)	1.41 (1.00–1.98; $p = 0.052$)	1.29 (0.96–1.74; $p = 0.122$)
Distant recurrence	1.02 (0.64–1.61; $p = 0.938$)	0.73 (0.58–0.92; $p = 0.009$)	0.77 (0.61–0.97); $p = 0.028$)	0.78 (0.63–0.96; $p = 0.023$)

TNT total neoadjuvant therapy, *RCT* randomized controlled trial, *pN+* positive pathological nodes (pN1 and above)

preoperative chemoradiation has come into question, with multiple RCTs showing no long-term survival benefits.[5,7] The lack of treatment effect and part of the challenge with adjuvant chemotherapy is poor patient tolerance following LCCRT and TME surgery. This was evident in the EORTC

Author and Year	TNT (+)	TNT (−)	NCRT (+)	NCRT (−)	Weight		Odds Ratio [95%CI]
Bahadoer et al., 2020	29	397	17	383	46.9		1.65 [0.89, 3.04]
Markovina et al., 2017	6	63	3	66	7.8		2.10 [0.50, 8.74]
Bujko et al., 2016	35	226	18	236	45.3		2.03 [1.12, 3.69]
Total	70 (9.3%)	686 (90.7%)	38 (5.3%)	686 (94.7%)	100%		
Pooled Odds Ratio							1.86 [1.23, 2.80]

Heterogeneity:I2=0.00%, p−value=0.877
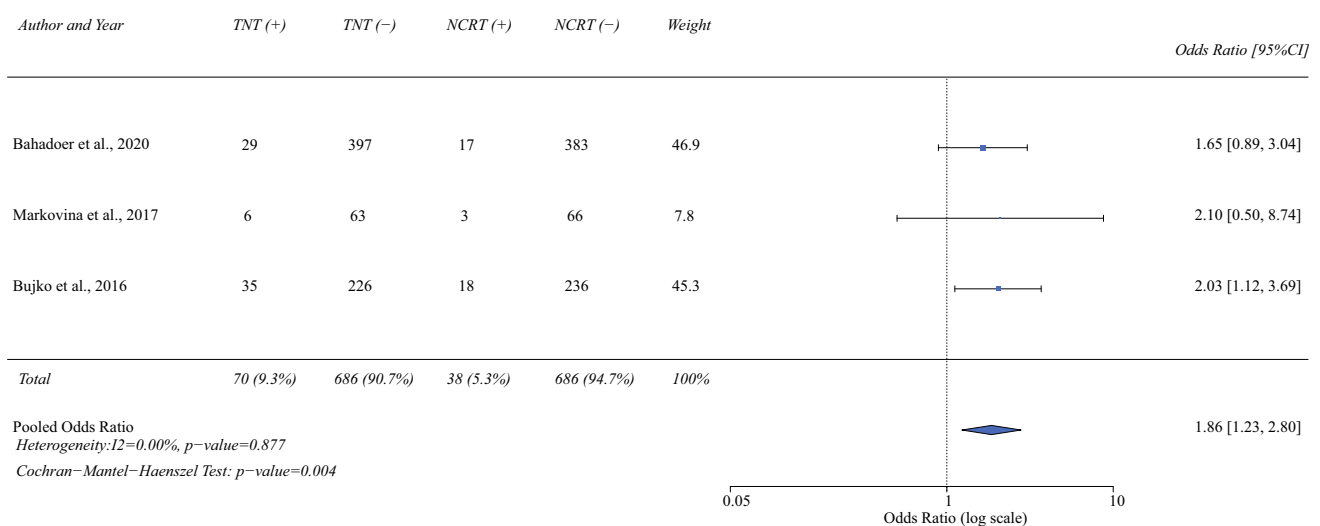Cochran−Mantel−Haenszel Test: p−value=0.004

FIG. 5 Consolidation TNT subanalysis, comparing rate of local recurrences in total neoadjuvant therapy versus standard neoadjuvant chemoradiotherapy

22921 trial, which showed only 43% of patients received the planned dose within the scheduled time interval.[5]

To overcome this issue, the proponents of TNT seek to improve chemotherapy compliance by delivering all treatment preoperatively rather than postoperatively when patients are disadvantaged from the morbidity and lower performance status associated with major surgery. In this study, compliance was not measured as it was only reported in three studies.[18,21,37] From these, both Cercek et al.[18] and Fernandez-Martos et al.[37] showed a superior compliance rate in the TNT group, achieving a rate of 96% and 94%, respectively, compared with 88% and 57% in the nCRT group. Similarly, the unpublished PRODIGE 23 phase III RCT by Conroy et al. showed a compliance rate for TNT of 91.6% versus 75.3% for adjuvant chemotherapy following nCRT.[21] This study also demonstrated a significant improvement in 3-year DSF in favor of the TNT approach (75.7% vs. 68.5%). It should be noted that this advantage could also come from the fact that patients in the TNT group received FOLFIRINOX instead of FOLFOX and received overall, more cycle of chemotherapy than the patients in the CRT group. It is often said that TNT has the advantage of targeting micrometastases early in the disease process. Our analysis confirms this with a lower incidence of distant recurrences which is the main driver of the overall survival advantage observed in our pooled analysis.

The chemotherapy strategies employed in TNT have involved combination regimens administered either before (induction therapy) or after (consolidation therapy) radiotherapy. In most studies, the median interval time to surgery was 4–11 weeks after last dose of treatment. However, it should be noted that those studies that employed consolidation TNT resulted in a longer wait from completion of radiotherapy to surgery. For example, the RAPIDO trial by Bahadoer et al., which reported a median time of 20–22 weeks,[31] and Marco et al. with a reported median time of 14–25 weeks from completion of radiotherapy.[28] Hence, the efficacy and safety profile of the new TNT strategy (resulting in a longer wait but receiving consolidation chemotherapy) specific to surgery was assessed in this metaanalysis. First, the longer wait from the two above-mentioned studies resulted in much higher pCR rates of 28.4% and 38.5%, respectively. Critically important, Bahadoer et al. showed that, despite the long interval wait for surgery, the TNT group achieved an equivalent R0 resection margin and a significant survival advantage in terms of the risk of distant recurrence.[31] It is worth reminding that in the GRECCAR-6 trial, a longer interval time to surgery after CRT (11 vs. 7 weeks) had resulted in similar pCR rates but increased postoperative complications and worse TME quality. Reassuringly, TNT in the RAPIDO trial does not increase postoperative morbidity despite a longer interval time to surgery. The rates of

anastomotic leak, wound complications, bleeding, and deep surgical site infection were equivalent between the two groups. Because of the paucity and heterogeneity of the reported data, other perioperative safety metrics of the TNT approach could not be evaluated in this metaanalysis. Nevertheless, data from the unpublished PRODIGE23 trial presented at ASCO2020 demonstrates a similar median hospital stay and rate of overall postoperative morbidity whether TNT or standard LCCRT was used. Moreover, in this study, patients in the TNT group were less likely to undergo a nontherapeutic laparotomy either because of metastatic disease or unresectable primary. Postoperative mortality was also higher in the CRT group (2.8%) versus the TNT group (0%).

One of the interesting observations of our metaanalysis is that, when pooled together, the studies that used short course radiation in their consolidation-type TNT protocol had an 86% increase in local recurrences compared with CRT. Overall, the rate of local recurrence was still low for LARC, with 9.3% versus 5.3% in the pooled SRT TNT and CRT groups, respectively. Nevertheless, this suggests that the additional downstaging expected with long-course CRT is probably the preferred radiation protocol for rectal cancer at higher risk of local recurrence such as T4 disease. On the other hand, short course radiation has its advantages in terms of health costs and patient convenience. Therefore, it is thus a valid option for tumors at lower risk of local recurrence. Since all the studies with local recurrence data in the consolidation TNT subgroup all used short course radiation, it is difficult to ascertain whether the increased local recurrences are due to the radiation protocol used or because of the consolidation sequence with the inherent longer wait time between the end of radiation and surgery. In the unpublished OPRA trial (ClinicalTrials.gov identifier: NCT02008656) the only difference between the two TNT groups was the sequencing of chemotherapy and CRT. Preliminary data from this trial do not suggest that the sequence of chemotherapy affects the rate of local recurrences, although pCR rates were higher with consolidation chemotherapy.

Although this metaanalysis demonstrates improvements in pCR, nodal downstaging, anal preservation, and resection margin with TNT, it should be remembered that the current practice remains a blanket approach for all patients with locally advanced rectal cancer regardless of their risk of distant metastasis. Without pathological information such as tumor morphology, nodal positivity, and lymphovascular invasion (high-risk features for distant metastasis), current stratification relies on radiological evidence such as T4a/b, EMVI positivity and nodal positivity in the mesorectum or lateral pelvic sidewall on MRI as eluded in the RAPIDO trial.[31] Therefore, further validation in selecting the most appropriate patient for the TNT

approach is required to balance the risk of distant metastasis against the morbidity associated with overtreatment in the form of additional chemotherapy. On the other hand, if safety can be demonstrated, an organ-preservation approach is possible in a higher proportion of patients who receive TNT compared with standard CRT, and this could counterbalance the effects of overtreating some patients who are overstaged by preoperative MRI.

As more data emerges, it is clear that any long-term survival advantage of TNT over standard CRT is through a lower rate of distant recurrences. Our induction and consolidation subanalyses (Table 2) found that only consolidation-type TNT was associated with a statistically significant lower rate of distant recurrences when compared with non-TNT neoadjuvant protocols. The German CAOAROAIO-12 phase II randomized trial compared induction to consolidation-type TNT in stage II and III rectal cancer to pick the best approach for their subsequent CAOAROAIO-18 phase 3 trial comparing TNT with standard of care. In CAOAROAIO-12, only the consolidative chemotherapy group met the prespecified primary end point of a 25% pCR rate (17% pCR with induction chemotherapy and 25% pCR with consolidative chemotherapy). In the unpublished OPRA trial, with a 2.1-year median follow-up, DFS did not seem to be affected by the chemotherapy and radiation sequence. Overall, 77% of the patients in the consolidation chemotherapy group were free of disease at 3 years, compared with 78% in the induction group. There was a significant difference in organ preservation between the two groups, again in favor of the radiation first approach (58 versus 43%, $p = 0.01$).

There are several limitations to this metaanalysis. First is the TNT protocol heterogeneity, including three studies that used short-course radiotherapy, and hence it is not clear which regimen would give the maximum oncological benefit. Second is the inclusion of nonrandomized observational studies. Third, the analysis only included 3-year oncological outcomes as this was the most commonly reported data point, therefore more mature data will need to be accumulated to determine the true effect on overall survival. Fourth, is that there were only a few studies that had reported on anastomotic leak, with no reported definitions on how anastomotic leak was diagnosed. As an anastomotic leak is a key surgical outcome, particularly with extended chemotherapy with potential immunosuppressive side effects, this would be an important endpoint to document in future studies. Fifth, the only postoperative complication that was consistently reported was anastomotic leak. Other operative outcomes such as surgical site infections, estimated blood loss, medical complications, and length of stay are a few indicators that are equally important and were rarely reported.

CONCLUSIONS

The current pooled data have shown that TNT has an immediate positive effect on rectal cancers, in particular downstaging of both the primary site and nodal basin with the added benefit in the rate of anal preservation, distant recurrences, disease-free survival, and 3-year overall survival. Our subanalyses have given some idea on the optimal TNT protocol. Long-course chemoradiotherapy followed by consolidation chemotherapy appears to be a preferable protocol for patients with LARC. In fact, this is the protocol that will be compared with standard CRT in the awaited CAOAROAIO-18 trial as well as the watch and wait JANUS trial. As more RCTs mature, we will have better clarity regarding the potential benefit of TNT on long-term survival. The favorable oncological outcomes of TNT combined with its practical advantages, such as reducing the rate of APR, the time with a stoma,[18] and testing the tumor's sensitivity to chemotherapy agents, potentially makes it the favored approach for locally advanced rectal cancer. TNT is already becoming much more prevalent, and some argue that it should be considered the new standard of care for LARC.[38] As we await long-term survival data, it is important that we work on identifying the patient group that will benefit most from the TNT approach. Like in breast cancer, categorizing rectal cancer according to several biomarkers like MMR status and RAS/RAF mutation could potentially help us to tailor neoadjuvant therapy for each patient, thereby maximizing outcomes and limiting unnecessary toxicity.

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