

Total Neoadjuvant Therapy in Comparison with Conventional Treatment in the Management of Rectal Adenocarcinoma: A Systematic Review and Meta-analysis

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Abstract

Aim: This systematic review and meta-analysis aimed to compare total neoadjuvant therapy vs conventional treatment in the management of rectal adenocarcinoma. **Methods:** Seventeen high quality Randomization Clinical Trial studies with 8019 individual data, were entered in meta-analysis study, which reported 3 year DFS and/or OS in rectal adenocarcinoma patients. Pooled estimates of 3 year DFS and OS for various approach of treatment were obtained by calculating the weighted percent from studies. **Results:** The pooled estimates of DFS and OS rate during of 36 month follow up was 0.69 (0.95 CI 0.68, 0.70) and 0.83(0.95 CI 0.83, 0.85) to 6 type treatment approach in rectal adenocarcinoma patients. Subgroup analysis shows higher and lower overall DFS rate was 0.73 (0.95 CI 0.65, 0.79) for two approach (CT-CRT-S and CRT-CT-S) and 0.645 (0.95 CI 0.59, 0.70) (RT-CT-S). also higher and lower 3 year OS rate were 0.92 (0.95 CI 0.86, 0.95) in CRT-CT-S and 0.80 (0.95 CI 0.78, 0.83) in CRT-S approach ($p<0.05$). **Discussion:** PCR and sphincter preservation are the most frequently reported outcome benefits of TNT in various trials. However, due to the heterogeneous patient populations in each study, which include high-risk features and differing treatment schedules, the survival advantage is not universally applicable. Therefore, the decision to use TNT should be tailored to the individual patient and made within a multidisciplinary framework. Despite this uncertainty, the use of TNT in rectal cancer continues to be explored as a means of enhancing patient outcomes and improving quality of life.

Keywords: Total neoadjuvant therapy- induction chemotherapy- neoadjuvant chemoradiotherapy- adjuvant chemotherapy

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1. Introduction

Rectal cancer ranks among the most prevalent cancers worldwide. While the traditional standard of care for managing patients with locally advanced (clinical

T3–4 or N-positive) rectal cancer included neoadjuvant chemoradiotherapy, definitive surgery, and adjuvant chemotherapy, recent years have seen a growing shift

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towards administering all treatments before surgery [1, 2]. This approach, known as total neoadjuvant therapy (TNT), has resulted in increased rates of pathologic complete response (pCR), improved chemotherapy completion rates, and has been associated with higher disease-free survival (DFS) [1, 3].

TNT has been implemented in various methods, including variations in the radiotherapy schedule, chemotherapy regimen, and their sequence of administration [2]. In terms of the radiotherapy schedule, POLISH II (2019) [4], RAPIDO (2020) [3] and STELLAR (2022) [5] trials employed short-course radiotherapy, while PRODIGE-23 (2020) [1], CAO/ARO/ AIO-12 (2019) [6] and OPRA (2020) trials utilized long-course radio-chemotherapy. In contrast, only the PRODIGE-23 (2020) trial incorporated the FOLFIRINOX chemotherapy regimen, with the others opting for the conventional FOLFOX/CAPOX regimens [1, 3-7].

Regardless of methods, these trials showed that TNT is a promising option in the management of patients with rectal cancer. This systematic review and meta-analysis aimed to compare total neoadjuvant therapy against conventional treatment in the management of rectal adenocarcinoma.

2. Methods

2.1. Study design

This meta-analysis was conducted per the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guideline [8]. In this study included clinical trial [9] and randomized clinical trial (RCT) studies, that comparing efficacy of TNT or CT-CRT-S with standard approach (CRT-S-CT) in the management of patients with rectal adenocarcinoma in terms of Clinical outcomes pCR, disease-free survival (DFS), overall survival (OS), and acute complications of chemoradiotherapy and surgery, pathological response and preservation of the sphincter.

2.2. Search strategy

The electronic search was limited to English articles published from 2012 onwards. To avoid a literature missing, two auteurs independently searched for free-text and standard MeSH terms in PubMed, Web of Science, Scopus, and Embase up to November 22, 2023 (11 past years).

Rectal malignancies OR Rectal adenocarcinoma OR Neoadjuvant chemotherapy OR total neoadjuvant treatment were keywords search. Also, hand searched conducted by the two authors in the reference lists of the relevant articles to identify the possible missed RCTs. After the removed title duplicates, two authors independently excluded studies according to irrelevant title and abstract, they debated on the disagreements to improve the results. Eventually, the methodological and quality of each included RCT was assess by Jadad scale. Scores on the Jadad scale range from 0 to 5. Articles with a Jadad score ≥ 3 was considered high quality and entered to meta-analysis (Figure 1).

2.3. Study screening

2.3.1. Participants

Studies on patients with rectal adenocarcinoma, clinical T3/T4, no evidence of distant metastasis or secondary malignancy, surgery were included (Table 1).

2.3.2. Inclusion criteria

We included RCTs (Phase 3/2) or CTs comparing Total Neoadjuvant chemotherapy Treatment (TNT) and standard Treatment.

2.3.3. Exclusion criteria

Studies were excluded if (a) only reported of protocol study, (b) only Radiotherapy/ chemotherapy conducted prior to surgery (c).

2.4. Data extraction

The following data were extracted from the studies: (i) study information (the first author, year of publication, study country, sample size), patient baseline characteristics (age, sex ratio), (iii) intervention duration and treatment outcomes (OS and PFS rate in 36 month follow up).

2.5. Quality assessment

Two investigators (S.A.J. and F.A) assessed the methodological quality and risk of bias of the included studies. All 33 included studies assessed using Jadad tool. They resolved differences by discussion or by appeal to a third review author and presented results in a 'Risk of bias' table. Risk of bias summary consists of 3 questions about randomization (0–2 points), blinding (0–2 points), dropout and withdrawal (0–1 points). Scores on the Jadad scale range from 0 to 5. Studies with a quality score less than 3 were regarded as poor quality and excluded from this study.

2.6. Statistical analysis

The main objective of this meta-analysis was to compare the efficacy of total neoadjuvant treatment with standard approach in the management of patients with rectal adenocarcinoma in terms of present weighted of OS and DFS to estimate the pooled present and 95% confidence interval (95% CI) of DFS and OS in each group of RCTs. and acute complications of chemo radiotherapy and surgery, pathological response. The statistical heterogeneity between studies was evaluated using Cochran's Q test and quantified by I² statistics. For statistical analyses, we applied by Comprehensive Meta-Analysis Software. The statistical significance level was set to 0.05.

Results

33 high quality studies with 13355 individual data were entered in review study. 17 studies with 8019 individual data, include of 35 data set were entered in meta-analysis study.

These data were included 6 subgroup treatment approaches (CRT-S, n=1280, CT-CRT-S, n=143,

Table 1. Characterizes of Included Study in Meta-analysis

	Study	Design	Total n	Type of treatment	n	DFS rate	OS rate
1	Jung, Minkyu , 2015 [10]	RCT P2	141	CRT-S-CT	A&B=116	0.78	0.86
2	Breugom, AJ, 2015 [11]	RCT P3	437	CRT- S	A=221	0.52	0.85
				CRT -S-CT	B=216	0.6	0.87
3	Lefèvre, Jérémie 2019 [12]	RCT P3	253	CRT-S-CT	B=263	0.67	0.895
4	Bosset, Jean-François 2014 [13]	RCT P3	1011	CRT -S	B=253	0.65	0.5
				CRT-S-CT	D=253	0.66	0.48
5	Fokas, Emmanouil, 2022 [14]	RCT P2	311	CT-CRT-S	A=143	0.73	0.9
				CRT-CT-S	B=143	0.73	0.92
6	Azria, D 2017 [15]	RCT	584	CRT-S-CT	A=293	0.7	0.86
7	Bujko, Krzysztof [16]	RCT	515	CRT-S	B=254	0.52	0.65
8	Conroy, Thierry 2021 [1]	RCT P3	461	CRT-S-CT	A&B=461	0.72	0.89
9	Hong, Yong Sang 2019 [9]	RCT	321	CRT-S-CT	A&B= 321	0.7	0.86
10	Schmoll, Hans-Joachim 2021 [17]	RCT	1094	CRT-S-CT	A&B=1094	0.76	0.87
11	Latkauskas, Tadas 2016 [18]	RCT	150	CRT-S-CT	A=72	0.75	0.82
				RT-S-CT	B=68	0.59	0.78
12	Ngan, Samuel Y 2012 [19]	RCT	326	RT-S-CT	A=160	0.7	0.8
				CRT-S-CT	B=161	0.73	0.78
13	Fan, Wen-Hua 2015 [20, 21]	RCT	192	CRT-S	A=90	0.87	0.92
14	Bahadoer, Renu R 2021 [3] [22]	RCT	912	CT-RT-S-CT	A=460	-	0.89
				CRT-S-CT	B=450	-	0.88
15	Valentini, Vincenzo 2019 [23]	RCT	534	CRT-S	A&B=402	0.8	0.9
16	Senyurek, Sukran 2023 [24]	RCT	140	CRT-S	A&B=60	-	0.88
17	JIN, Jing, 2022 [5]	RCT	599	RT-CT-S	A=302	0.64	0.86
				CRT-S-CT	B=297	0.62	0.75

CRT-CT-S, n=143, RT-S-CT, n=228, CRT-S-CT, n=3578, RT-CT-S, n=302) for determinate of 3 years DFS rate in rectal adenocarcinoma patients (n=5614).

In this data higher and lower DFS rate were 0.88 (0.95 CI 0.80, 0.93) and 0.52 (0.95 CI 0.45, 0.58) that both result belonged to unstandard approach (CRT-S). Overall DFS rate during of 36 month follow up was 0.69 (0.95 CI 0.68, 0.70) in these patients (fixe model) Figure 2-1. Subgroup analysis according to treatment approach (6 type) shows, higher overall DFS rate was 0.73 (0.95 CI 0.65, 0.79) for two approach (CT-CRT-S and CRT-CT-S) [14]. Strong confidence interval (0.95) for overall DFS was belonged to standard approach group (0.71 CI 0.69, 0.72). lower overall DFS rate was 0.645 (0.95 CI 0.59, 0.70) in patients that treated by RT-CT-S approach (1 studies) (Figure 2-2), although heterogeneity was seen within and between studies $p < 0.001$.

Also 3 years OS rate described in patient with 6 varied treatment approach (CRT-S, n=1280, CT-CRT-S, n=143, CRT-CT-S, n=143, RT-S-CT, n=228, CRT-S-CT, n=3615, CT-RT-S-CT, n=460) in rectal adenocarcinoma patients. Higher 3 years OS rate (0.92) was seen in 2 treatment approach CRT-CT-S and CRT-S (Figure 3-1). Figure 3-2 shows, three years pooled overall survival was 0.83 (0.95 CI 0.83, 0.85) in these patients. In compared pooled overall survival rate between 6 treatment group, higher and lower rate were 0.92 (0.95 CI 0.86, 0.95) in CRT-CT-S and 0.80 (0.95 CI 0.78, 0.83) in CRT-S treatment approach ($p < 0.05$).

Comparison of DFS according to treatment approach shows there is no significant difference in DFS rate (three years) for standard treatment (CRT-S-CT) and two similar treatments (CT-CRT-S & CRT-CT-S) Figure 4.

Discussion

Total neoadjuvant treatment (TNT) is a multidisciplinary approach that has gained increasing attention in recent years as a promising strategy for improving treatment efficacy in rectal cancer. This approach has been shown to improve some oncological outcomes, but there is ongoing debate regarding its potential survival advantage. In this meta-analysis, we included all clinical trials that investigated any of the mentioned treatment protocols for rectal cancer in terms of OS, 3years DFS, PCR, and sphincter preservation. There is a large amount of heterogeneity for pooled 3 years DFS and OS rate in CRT-S trials ($I^2=96.740$ and 94.402 , p -value:0.00, respectively) and CRT-S-CT trials ($I^2=78.674$ and 81.829 , p -value:0.00, respectively).

TNT approach has several approved benefits, including improved patient treatment compliance, enhanced quality of life due to organ preservation, and superior PCR. PCR rate with the TNT approach is reported to be between 12% and 36%, while it ranges from 5.4% to 21% for conventional CRT-S-CT [supplement 4] The rate of organ preservation is also higher in TNT approaches (CRT-CT-S and CT-CRT-S) [supplement 6]. In terms of two different

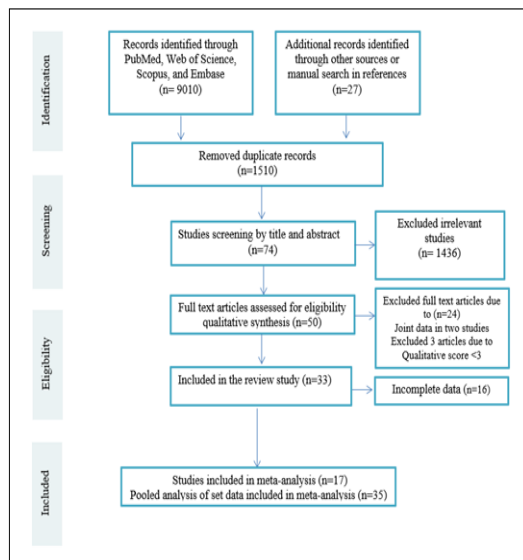


Figure 1. PRISMA Flow Diagram

schedules of TNT, the enhancement of PCR and organ preservation is more clearly defined in the consolidation chemotherapy approach [6] [supplement 6]. A subject of interest regarding the achievement of PCR using the TNT approach is the comparison between short-course RT and long-course CRT. The STELLAR trial reported better PCR utilizing short-term radiotherapy followed by double-agent consolidative chemotherapy (six cycle CAPOX) (RT-CT×4-S-CT×2) compare with long course CRT-S-CT×6 (21.8% vs. 12.3%, $P=.002$ respectively) [5]. However, the POLISH II trial, which investigated the TNT approach with short-term radiotherapy and consolidative double-agent chemotherapy (3 cycle FOLFOX), did not

demonstrate any benefits in either PCR (16% with TNT vs. 12% with CRT, $p = 0.17$) or survival endpoints compared to long course CRT-S [16]. In the RAPIDO trial also short course radiotherapy was administered but with longer duration of consolidative chemotherapy in TNT approach and despite POLISH II trial, it showed better PCR versus conventional CRT-S-CT [3].

Beyond the discussion of PCR, there is some debate and controversies about the survival benefit of TNT approach. Variations in treatment schedules, chemotherapeutic agents (triple vs. double agent regimens), duration of chemotherapy, and radiotherapy regimens (long course vs. short course) across different clinical trials have led to differences in oncological outcomes. In our analysis, there is no significant difference in 3-year DFS rate of standard treatment (CRT-S-CT) and two similar TNT approaches (CT-CRT-S & CRT-CT-S) (Figure 4). Overall DFS rate is 0.70 (0.95 CI 0.69, 0.72). The undermost DFS rate is 0.52 (0.45-0.58) belonging to CRT-S, a non-standard approach. And the highest overall DFS rate, is 0.73 (0.95 CI 0.65, 0.79) belonging to the TNT approach that is reported in CAO/ARO/AIO-12 trial [14]. Long-term results of this trial have raised questions about the association of enhanced PCR with survival benefits [6]. Also, Goffredo et al.'s retrospective study found that survival rates for TNT were lower than for CRT, but TNT showed a higher PCR rate [25]. It indicates that one should exercise caution when generalizing the advantages of the TNT approach to survival outcomes. [26]. The PRODIGE23 trial investigated the TNT approach with triplet induction chemotherapy and long course chemoradiation, showing the first evidence of improved survival rates (OS, DFS, 5-year distant metastasis-free survival, 5-year cancer-

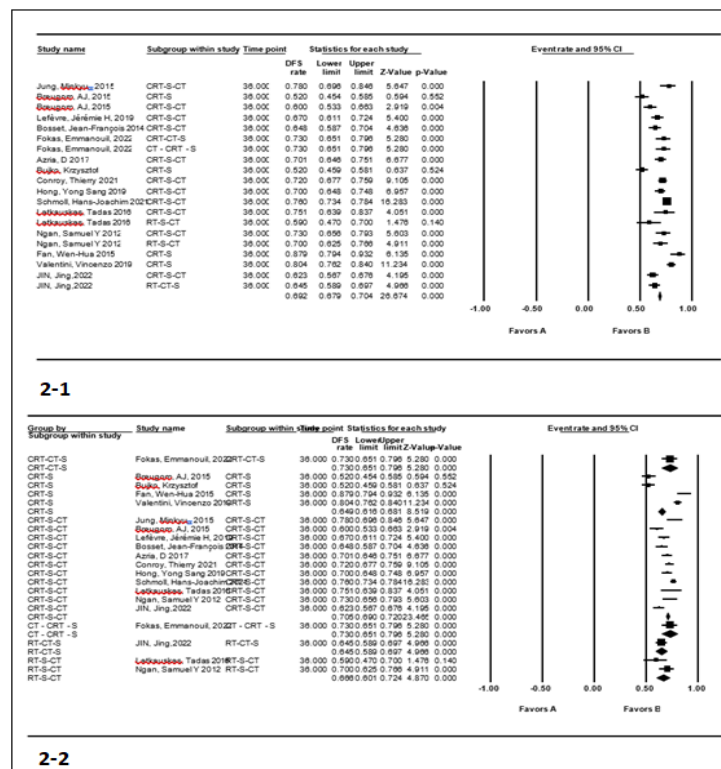


Figure 2. 2-1, Forest Plot of Overall Three Years DFS Rate in Rectal Adenocarcinoma Patients $\tau = 0.37$, $p < 0.001$. 2-2, Subgroup analysis of overall three years DFS rate in rectal adenocarcinoma patients

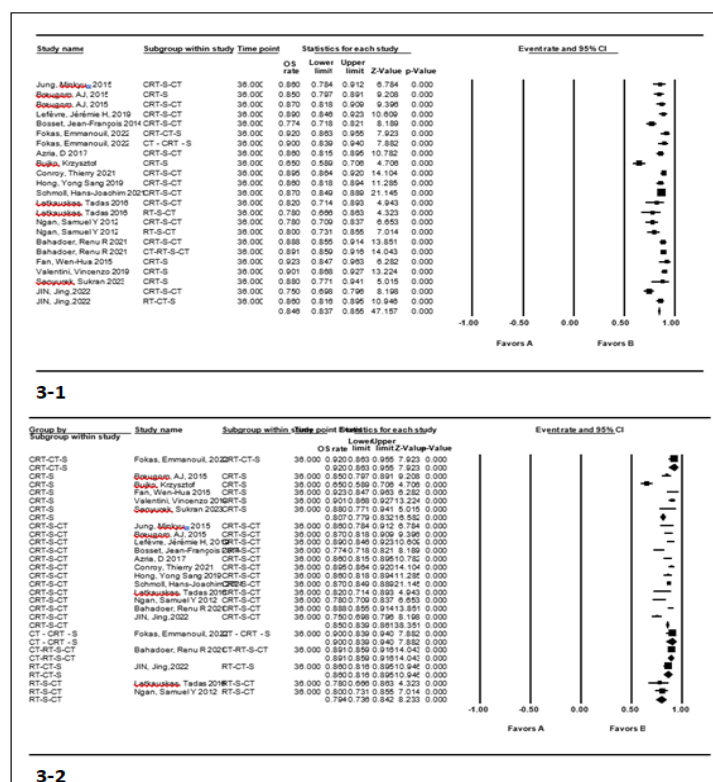


Figure 3. 3-1, Forest Plot of Pooled Three Years OS Rate in Rectal Adenocarcinoma Patients Tau=0.44, $p < 0.001$. 3-2, Subgroup analysis of pooled three years OS rate according to type of approach treatment in rectal adenocarcinoma patients

specific survival).

Another subject that has been investigated regarding the treatment of rectal cancer and has sparked enthusiasm for using the TNT approach is omitting surgery in patients who achieve PCR. Long term results of phase II OPRA trial which is published recently after 5.1 years' follow-up shows similar DFS between patients who underwent TME after TNT approach or underwent TME after regrowth during watch and wait approach [27]. OPRA trial was the first prospective RCT that examined organ preservation with TNT approach using double agent chemotherapy. In this trial also regrowth rate and TME free survival rate were in favor of consolidative chemotherapy arm.

The differences in outcome benefits observed in trials may be attributed to heterogeneity in inclusion criteria, as

well as the percentage of patients with high-risk features included in the studies. However, regarding established benefit of TNT to reach PCR, the most applicable patient for TNT are middle and low rectal tumors in which sphincter preservation has been challenging for a long time. Treatment protocol like RODIGE23 may be better for patients with high-risk features (extramural vascular invasion (EMVI), significant lymphadenopathy (cN2), multiple lateral lymph nodes enlargement, and/or cT4 tumor, CRM < 1 mm, MRF+) while OPRA trial protocol is suitable for others [1].

In conclusion, PCR and sphincter preservation are the most frequently reported outcome benefits of TNT in various trials. However, due to the heterogeneous patient populations in each study, which include high-risk features

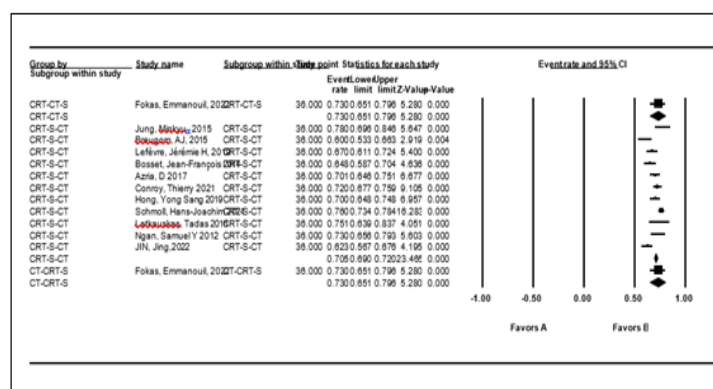


Figure 4. Comparison of Three Years DFS Rate in Standard Treatment (CRT-S-CT) and Two Similar Treatments (CT-CRT-S & CRT-CT-S) in Rectal Adenocarcinoma Patients. This fig wasn't reported significant heterogeneity between these approaches $p = 0.67$. overall DFS was 0.70 (0.95 CI 0.69, 0.72).

and differing treatment schedules, the survival advantage is not universally applicable. Therefore, the decision to use TNT should be tailored to the individual patient and made within a multidisciplinary framework. Despite this uncertainty, the use of TNT in rectal cancer continues to be explored as a means of enhancing patient outcomes and improving quality of life.

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Data Availability Statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author/s.

Ethics Statement

The Ethic Committee of Sabzevar University of Medical Sciences approved the study protocol (ID IR.MEDSAB.REC.1401.022).

Author Contributions

Conceptualization; S.A.J., F.A., Data curation; F.A. P.M., Funding acquisition; S.A.J., Investigation; P.P., B.P., M.A., Me.M., Ma.M., J.W., S.A.J., F.A., Methodology; S.A.J., F.A., Project administration; S.A.J., F.A., Software; F.A., Supervision; S.A.J., P.P., B.P., Validation; J.W., Visualization; Me.M., Ma.M., Roles/Writing original draft; P.M., P.R., Writing - review & editing; P.P., B.P., M.A., Me.M., Ma.M., J.W., S.A.J., F.A.

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Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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