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Review and Meta-analysis

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

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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.

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 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).

Figure 1. PRISMA Flow Diagram.

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).

	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 CRT -S-CT	A=221 B=216	0.520.6	0.850.87
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 CRT-S-CT	B=253D=253	0.650.66	0.50.48
5	Fokas, Emmanouil, 2022 [14]	RCT P2	311	CT-CRT-S CRT-CT-S	A=143 B=143	0.730.73	0.90.92
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 RT-S-CT	A=72 B=68	0.750.59	0.820.78
12	Ngan, Samuel Y 2012 [19]	RCT	326	RT-S-CT CRT-S-CT	A=160 B=161	0.70.73	0.80.78
13	Fan, Wen-Hua 2015 [20, 21]	RCT	192	CRT-S	A=90	0.87	0.92
14	Bahadoer,	RCT	912	CT-RT-S-CT	A=460 B=450		0.890.88

	Renu R 2021 [3] [22]			CRT-S-CT			
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 CRT-S-CT	A=302 B=297	0.640.62	0.860.75

Table 1. Characterizes of Included Study in Meta-analysis.

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,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 bilonged 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.

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.

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. 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.

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-Streatment 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.

Figure 4. Comparison of Three Years DFS Rate in Standard Treatment (CRT-S-CT) and Two Similar Treatments (CT-CRT-S and 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).

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 (I2=96.740 and 94.402, p-value:0.00, respectively) and CRT-S-CT trials (I2=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 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, Goffreddo 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-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 stablished 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 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.

References

References

1. Conroy T, Bosset JF, Etienne PL, Rio E, François É, Mesgouez-Nebout N, Vendrely V, et al. Neoadjuvant chemotherapy with FOLFIRINOX and preoperative chemoradiotherapy for patients with locally advanced rectal cancer (UNICANCER-PRODIGE 23): a multicentre, randomised, open-label, phase 3 trial. *The Lancet. Oncology.* 2021; 22(5)DOI
2. Johnson GGRJ, Park J, Helewa RM, Goldenberg BA, Nashed M, Hyun E. Total neoadjuvant therapy for rectal cancer: a guide for surgeons. *Canadian Journal of Surgery. Journal Canadien De Chirurgie.* 2023; 66(2)DOI
3. Bahadoer RR, Dijkstra EA, Etten B, Marijnen CAM, Putter H, Kranenbarg EM, Roodvoets AGH, et al. Short-course radiotherapy followed by chemotherapy before total mesorectal excision (TME) versus preoperative chemoradiotherapy, TME, and optional adjuvant chemotherapy in locally advanced rectal cancer (RAPIDO): a randomised, open-label, phase 3 trial. *The Lancet. Oncology.* 2021; 22(1)DOI
4. Ciseł B., Pietrzak L., Michalski W., Wyrwicz L., Rutkowski A., Kosakowska E., Cencelewicz A., et al. Long-course preoperative chemoradiation versus 5 × 5 Gy and consolidation chemotherapy for clinical T4 and fixed clinical T3 rectal cancer: long-term results of the randomized Polish II study. *Annals of Oncology: Official Journal of the European Society for Medical Oncology.* 2019; 30(8)DOI
5. Jin J, Tang Y, Hu C, Jiang L, Jiang J, Li N, Liu W, et al. Multicenter, Randomized, Phase III Trial of Short-Term Radiotherapy Plus Chemotherapy Versus Long-Term Chemoradiotherapy in Locally Advanced Rectal Cancer (STELLAR). *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology.* 2022; 40(15)DOI
6. Fokas E, Allgäuer M, Polat B, Klautke G, Grabenbauer GG, Fietkau R, Kuhnt T, et al. Randomized Phase II Trial of Chemoradiotherapy Plus Induction or Consolidation Chemotherapy as Total Neoadjuvant Therapy for Locally Advanced Rectal Cancer: CAO/ARO/AIO-12. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology.* 2019; 37(34)DOI
7. Garcia-Aguilar J, Patil S, Kim JK, Yuval JB, Thompson H, Verheij F. Preliminary results of the organ preservation of rectal adenocarcinoma (OPRA) trial. *J Clin Oncol.* 2020; 38:4008. DOI
8. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews.* 2015; 4(1)DOI
9. Salmenkylä S., Kouri M., Österlund P., Pukkala E., Luukkonen P., Hyöty M., Pääkkönen M., et al. Does preoperative radiotherapy with postoperative chemotherapy increase acute side-effects and postoperative complications of total mesorectal excision? Report of the randomized Finnish rectal cancer trial. *Scandinavian journal of surgery: SJS: official organ for the Finnish Surgical Society and the Scandinavian Surgical Society.* 2012; 101(4)DOI
10. Jung M, Shin SJ, Koom WS, Jung I, Keum KC, Hur H, Min BS, et al. A Randomized Phase 2 Study of Neoadjuvant Chemoradiaton Therapy With 5-Fluorouracil/Leucovorin or Irinotecan/S-1 in Patients With Locally Advanced Rectal Cancer. *International Journal of Radiation Oncology, Biology, Physics.* 2015; 93(5)DOI
11. Breugom A. J., Gijn W., Muller E. W., Berglund Å, Broek C. B. M., Fokstuen T., Gelderblom H., et al. Adjuvant chemotherapy for rectal cancer patients treated with preoperative (chemo)radiotherapy and total mesorectal excision: a Dutch Colorectal Cancer Group (DCCG) randomized phase III trial. *Annals of Oncology: Official Journal of the European Society for Medical Oncology.* 2015; 26(4)DOI
12. Lefèvre JH, Mineur L, Cachanado M, Denost Q, Rouanet P, Chaisemartin C, Meunier B, et al. Does A Longer Waiting Period After Neoadjuvant Radio-chemotherapy Improve the Oncological Prognosis of Rectal Cancer?: Three Years' Follow-up Results of the Greccar-6 Randomized Multicenter Trial. *Annals of Surgery.* 2019; 270(5)DOI

13. Bosset J, Calais G, Mineur L, Maingon P, Stojanovic-Rundic S, Bensadoun R, Bardet E, et al. Fluorouracil-based adjuvant chemotherapy after preoperative chemoradiotherapy in rectal cancer: long-term results of the EORTC 22921 randomised study. *The Lancet. Oncology.* 2014; 15(2)DOI
14. Diefenhardt M, Schlenska-Lange A, Kuhnt T, Kirste S, Piso P, Bechstein WO, Hildebrandt G, et al. Total Neoadjuvant Therapy for Rectal Cancer in the CAO/ARO/AIO-12 Randomized Phase 2 Trial: Early Surrogate Endpoints Revisited. *Cancers.* 2022; 14(15)DOI
15. Azria D., Doyen J., Jarlier M., Martel-Lafay I., Hennequin C., Etienne P., Vendrely V., et al. Late toxicities and clinical outcome at 5 years of the ACCORD 12/0405-PRODIGE 02 trial comparing two neoadjuvant chemoradiotherapy regimens for intermediate-risk rectal cancer. *Annals of Oncology: Official Journal of the European Society for Medical Oncology.* 2017; 28(10)DOI
16. Bujko K., Wyrwicz L., Rutkowski A., Malinowska M., Pietrzak L., Kryński J., Michalski W., et al. Long-course oxaliplatin-based preoperative chemoradiation versus 5 × 5 Gy and consolidation chemotherapy for cT4 or fixed cT3 rectal cancer: results of a randomized phase III study. *Annals of Oncology: Official Journal of the European Society for Medical Oncology.* 2016; 27(5)DOI
17. Schmoll H, Stein A, Van Cutsem E, Price T, Hofheinz BD, Nordlinger B, Daisne J, et al. Pre- and Postoperative Capecitabine Without or With Oxaliplatin in Locally Advanced Rectal Cancer: PETACC 6 Trial by EORTC GITCG and ROG, AIO, AGITG, BGDO, and FFCD. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology.* 2021; 39(1)DOI
18. Latkauskas T, Pauzas H, Kairevice L, Petrauskas A, Saladzinskas Z, Janciauskiene R, Gudaityte J, et al. Preoperative conventional chemoradiotherapy versus short-course radiotherapy with delayed surgery for rectal cancer: results of a randomized controlled trial. *BMC cancer.* 2016; 16(1)DOI
19. Ngan SY, Burmeister B, Fisher RJ, Solomon M, Goldstein D, Joseph D, Ackland SP, et al. Randomized trial of short-course radiotherapy versus long-course chemoradiation comparing rates of local recurrence in patients with T3 rectal cancer: Trans-Tasman Radiation Oncology Group trial 01.04. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology.* 2012; 30(31)DOI
20. Fan W, Wang F, Lu Z, Pan Z, Li L, Gao Y, Chen G, et al. Surgery with versus without preoperative concurrent chemoradiotherapy for mid/low rectal cancer: an interim analysis of a prospective, randomized trial. *Chinese Journal of Cancer.* 2015; 34(9)DOI
21. Zhu J, Liu A, Sun X, Liu L, Zhu Y, Zhang T, Jia J, et al. Multicenter, Randomized, Phase III Trial of Neoadjuvant Chemoradiation With Capecitabine and Irinotecan Guided by UGT1A1 Status in Patients With Locally Advanced Rectal Cancer. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology.* 2020; 38(36)DOI
22. Valk MJM, Marijnen CAM, Etten B, Dijkstra EA, Hilling DE, Kranenbarg EM, Putter H, et al. Compliance and tolerability of short-course radiotherapy followed by preoperative chemotherapy and surgery for high-risk rectal cancer - Results of the international randomized RAPIDO-trial. *Radiotherapy and Oncology: Journal of the European Society for Therapeutic Radiology and Oncology.* 2020; 147DOI
23. Valentini V, Gambacorta MA, Cellini F, Aristei C, Coco C, Barbaro B, Alfieri S, et al. The INTERACT Trial: Long-term results of a randomised trial on preoperative capecitabine-based radiochemotherapy intensified by concomitant boost or oxaliplatin, for cT2 (distal)-cT3 rectal cancer. *Radiotherapy and Oncology: Journal of the European Society for Therapeutic Radiology and Oncology.* 2019; 134DOI
24. Senyurek S, Saglam S, Saglam EK, Yanar H, Gok K, Tastekin D, Akbas CK, et al. Neoadjuvant intermediate-course versus long-course chemoradiotherapy in T3-4/N0+ rectal cancer: Istanbul R-02 phase II randomized study. *Oncology Research.* 2023; 31(5)DOI
25. Goffredo P, Suraju MO, Mott SL, Troester AM, Weaver L, Mishra A, Sokas C, Hassan I. Pathologic Complete Response, Total Neoadjuvant Therapy and the Survival Paradox in Locally Advanced Rectal Cancer. *Annals of Surgical Oncology.* 2024; 31(10)DOI
26. Romero Zoghbi SE, Martín Martín M, García JC, Valero M, Rincón D, Peña Huertas M,

Fusco JP, et al. Total Neoadjuvant Therapy Approach for the Treatment of Locally Advanced Rectal Cancer: Where Do We Stand?. *Oncology.* 2024; 102(7)DOI

27. Verheij FS, Omer DM, Williams H, Lin ST, Qin L, Buckley JT, Thompson HM, et al. Long-Term Results of Organ Preservation in Patients With Rectal Adenocarcinoma Treated With Total Neoadjuvant Therapy: The Randomized Phase II OPRA Trial. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology.* 2024; 42(5)DOI