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Current approaches in intensification of long-course chemoradiotherapy in locally advanced rectal cancer: a review

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Rectal cancer is one of the most prevalent cancers in the world. In many countries, the current standard of care is long-course chemoradiation (CRT), followed by total mesorectal excision. Some efforts have been made by intensifying radiation or chemotherapy components of the neoadjuvant therapy to further decrease the local recurrence and augment surgery's feasibility and improve the oncological outcomes. This paper reviews recent intensified neoadjuvant interventions in locally advanced rectal cancer (LARC) in terms of efficacy and treatment-related toxicity. Many maneuvers have been made so far to improve the oncological outcomes of rectal cancer with intensified neoadjuvant long-course CRT. Some of these approaches seem compelling and deserve further study, while some have just increased the treatment-related toxicities without evident benefits. Those endeavors with greater pathological complete response than the standard of care may make us await the long-term results on survival rates and chronic treatment-related toxicity. After introduction of neoadjuvant CRT for LARC there have been many efforts to improve its outcomes. Here, this study gathered most of these efforts that intensified the neoadjuvant therapy with some being promising and some being futile.

Keywords: Radiotherapy, Neoadjuvant therapy, Rectal cancer, Neoadjuvant therapy, Chemoradiotherapy

Introduction

Rectal cancer is one of the most prevalent types of cancers, affecting both men and women. Based on the GLOBOCAN 2018 report, rectal cancer is the 8th most diagnosed cancer and the 10th deadliest one [1]. Nearly 700 thousand new rectal cancer cases were diagnosed in 2018, which is estimated to be 60% higher in 2030. On the other hand, about 310 thousand deaths were caused by rectal cancer in 2018, which is expected to reach 480 thousand in 2030 [1,2]. A considerable proportion of patients with rectal cancer presents with the locally-advanced disease that confers poorer outcomes than the early-stage disease and mandates multi-disciplinary management.

Currently, the mainstay treatment for locally advanced rectal cancer (LARC) is total mesorectal excision (TME), either open or using minimally invasive methods like robotic or laparoscopic surgery [3]. Compared to the colon, the cancers of the rectum harbor distinct considerations, including the limited space to obtain sufficient margins and to dissect lateral lymph node in the true pelvis [3,4]. Due to these considerations, adjuvant chemoradiation (CRT) has increased the survival of rectal cancer patients and decreased the likelihood of local recurrence (LR). The delivery of CRT before surgery was suggested 15 years ago and showed that, with similar efficacy, it could decrease the long-term toxicities compared to the postoperative CRT. So, this approach became the standard of care. Besides, preoperative CRT reduces the tumor size, sterilizes the operation field from cancer cells, and augments the chance of sphincter preservation [5,6].

The standard neoadjuvant therapy in most parts of the world, including North America and Western Europe, is long-course CRT consists of 50–50.4 Gy radiotherapy (RT) in 5–5.5 weeks concurrently with intravenous 5-fluorouracil (5FU) or oral capecitabine [7-10]. Since the hallmark study by Sauer et al. [6] there have been many efforts to improve neoadjuvant treatment outcomes to enhance the pathological complete response (pCR) and reduce local and distant recurrence. These efforts, which are grouped under the title of intensification of neoadjuvant therapy, consist of any radiation dose maximization or using more systemic medications that are added to the standard regimen.

This study was aimed to provide an overview of the intensified approaches, their current states, and the efficacy of these approaches regarding the short- and long-term oncological outcomes.

Radiotherapy Intensification

Based on the dose-response models for rectal cancer that showed better responses obtained by increasing total radiation dose [11], various RT techniques have been introduced to deliver higher doses of external beam radiation to increase local control (Table 1). Despite the promising results in terms of feasibility and good toxicity profile, the impact of these techniques on long-term outcomes and survival is not clear.

One of the most studied RT techniques is delivering a boost dose to the gross tumor through external beam photons. The landmark trial of MD Anderson by Janjan et al. [12] was the first to document the feasibility and favorable rate of sphincter preservation with the addition of concomitant boost to the gross tumor versus the historical method of neoadjuvant CRT. In this study, patients received a 45-Gy pelvic RT plus continuous infusion 5FU (300 mg/m^2) for 5 days per week. In addition, a 7.5-Gy boost was administered to tumor plus 2–3 cm margin in 5 fractions during the last week with a 6-hour interval from the pelvic irradiation.

Yang et al. [13] investigated the efficacy and safety of a combined preoperative regimen, including volumetric modulated arc

Table 1. Radiotherapy intensification studies in locally advanced rectal cancer underwent neoadjuvant chemoradiation and oncologic outcomes and adverse effect

Study, year	Study arms	N	pCR	Toxicity	DFS	OS
Janjan et al. [12], 2000	Single arm: concomitant boost to tumor with 3DCRT	45	31%	Acceptable rate wound healing, in 20%	ND	ND
Hernando-Requejo et al. [14], 2014	Single arm: concomitant boost to mesorectum with IMRT	74	30.60%	Acute GI toxicity G3: 9.5% Acute GU toxicity G3: 5.4%	3-yr DFS: 95.4%	3-yr OS: 85.9%
Osti et al. [15], 2014	Single arm: concomitant boost to mesorectum with 3DCRT	65	17%	G3-4 Overall toxicity: 15%	3-yr DFS: 81%	3-yr OS: 86.8%
Alongi et al. [16], 2017	Single arm: concomitant boost to the hypermetabolic areas	40	ND	Acute GI toxicity G2: 15% Acute GU toxicity G2: 12.5%	1-yr DFS: 100%	1-yr OS: 100%
Badakhshi et al. [17], 2017	Retrospective: concomitant boost to mesorectum with 3DCRT	141	9.90%	No acute G3-4 GI & GU toxicity	3-, 5-, and 10-yr DFS rates were 91.4%, 88.9%, and 79.3%, respectively	3-, 5-, and 10-yr OS rates were 91.9%, 84.6%, and 52.9%, respectively
Wang et al. [18], 2019	CRT alone vs. CRT plus Concomitant boost and consolidation CAPOX	120	13.3% vs. 23.3% (p = 0.157)	G3-4 toxicities 18.3% vs. 25.0% (p = 0.016)	3-yr DFS: 56.0% vs. 68.8% (p = 0.349)	3-yr OS: 75.3% vs. 88.5% (p = 0.553)
Yang et al. [13], 2019	Single arm: concomitant boost to mesorectum with VMAT	26	32	Two cases with G3 dermatitis Overall G2: 53.8%, mostly hematological	ND	ND
Valentini et al. [11], 2019	Two arms: concomitant boost to bulky site vs. concurrent biweekly oxaliplatin	534	24.4% vs. 23.8% (NS)	Neurological any grade: 1.7% vs. 21.7% (G3: 0% vs. 0.5%; p < 0.001) Hematologic any grade: CAPOX 15% vs. 24.1% (G3: 0% vs. 1.3%; p = 0.04)	5-yr DFS: 74.7% vs. 73.8% (p = 0.444)	5-yr OS: 80.4% vs. 85.5% (p = 0.155)

pCR, pathological complete response; DFS, disease-free survival; OS, overall survival; 3DCRT, three-dimensional conformal radiotherapy; ND, not defined; IMRT, intensity-modulated radiation therapy; GI, gastrointestinal; GU, genitourinary; CRT, chemoradiotherapy; CAPOX, capecitabine and oxaliplatin; VMAT, volumetric modulated arc therapy; NS, not significant; G, grade.

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therapy (VMAT) along with a simultaneous integrated boost consisting of 58.75 Gy (2.35 Gy per fraction) to mesorectum and 50 Gy (2 Gy per fraction) for other pelvic lymph node stations, with concurrent capecitabine. In this single-arm study, good sphincter preservation and pCR rates were achieved. The initial results also revealed good tolerance and a low occurrence rate of adverse side effects.

The effect of integrated-boost using intensity-modulated radiation therapy (IMRT) on the pCR has also been investigated by Hernando-Requejo et al. [14]. In this single-arm study 46 Gy in 23 fractions was prescribed for the pelvic nodes and mesorectum and 57.5 Gy in 23 fractions was prescribed as the boost dose concurrently with oral capecitabine. The results revealed that the concomitant-boost was known to be a well-tolerated treatment, even though no specific differences in overall and disease-free survival in comparison with other studies were found in patients with pCR.

Osti et al. [15] in a retrospective single-arm study, evaluated the impact of concomitant boost to the high-risk area with three-dimensional conformal radiotherapy (3DRT) technique in rectal cancer patients. The boost dose was 10 Gy delivered in 10 fractions twice a week while the intermediate risk areas received 45 Gy in 25 daily fractions. The results indicated that the RT treatment intensification might have a positive biological effect. However, the results have not yet been confirmed, and a more extended follow-up period was claimed to be needed.

The role of RT dose intensification through integrated boost was also inspected in the study by Alongi et al. [16], which had a non-randomized design. It was a prospective study in LARC within 10 cm of the anal verge. The methods were described as using high-dose volumes receiving a 6-Gy boost, including the hyper-metabolic areas defined as maximal standardized

uptake value (SUV_{max}) over 5 within a co-registered positron emission tomography scan of the corresponding mesorectum. Prophylactic areas received 54 Gy in 30 fractions. Oral capecitabine were taken twice a day for 5 days every week. This technique seemed to be practicable. Although it was indicated that the sensitivity and specificity of SUV_{max} values were in association with the best node down-staging and downsizing, the initial outcomes of this study did not confirm any benefits in terms of tumor regression and response rate [16].

A retrospective study by Badakhshi et al. [17] described the effects of concomitant boost with 3DCRT on long-term clinical outcomes in LARC. All patients received 45 Gy with concurrent 5FU but some also had a 5.4-Gy boost to the mesorectum and the gross tumor volume. The authors suggested that the concomitant boost is associated with improved overall survival (OS). Interestingly, there were no significant differences in treatment-related toxicities between the standard and boost therapy [17]. However, the small group of patients who received the boost dose faded any possible conclusions.

On a randomized trial, Wang et al. [18] analyzed whether a more intensified CRT could yield a promising clinical result in LARC; patients were divided into two different groups. One received 50 Gy pelvic IMRT (Arm A), and the other obtained 50 Gy pelvic RT plus a concomitant 5 Gy boost (0.2 Gy per fraction) to the primary lesion, followed by a cycle of CAPOX (capecitabine plus oxaliplatin) 2 weeks after the end of CRT (Arm B). Both arms were given capecitabine 625 mg/m^2 and oxaliplatin 50 mg/m^2 as concurrent chemotherapy. The final results demonstrated the pCR advantage of the concomitant boost at the expense of delayed postsurgical wound healing. The authors believed this finding would warrant further attention.

A long-term analysis of the INTERACT trial investigated the two different intensification regimens of preoperative capecitabine-based CRT, in which the patients randomized into either a concomitant RT boost to the bulky tumor or to concurrent biweekly oxaliplatin (130 mg/m^2). All patients received 45 Gy in 25 fractions to the pelvis. The concomitant boost group received 10 Gy boost in twice weekly one-gray fractions. In conclusion, the concomitant boost group significantly obtained better tumor regression grade (TRG) patterns in the surgical specimen. Thus, no distinguishable differences were found in clinical outcomes between the two arms. Nevertheless, according to the boost efficacy on TRG along with its lower toxicity and good compliance, it should be considered a treatment of choice for clinical T3 lesions [11].

As discussed above, many studies have been carried out on the intensification of RT in rectal cancer. Although they stated promising findings in the short-term, we should wait for the long-term outcomes in LR, OS, and chronic toxicities of the treatments.

Concurrent Chemotherapy Intensification

Using systemic therapy concurrently with RT is usually done with lower doses than chemotherapy alone. These doses are known to have radio-sensitizing effect that make tumors more susceptible to the impact of RT. Numerous preliminary reports have been published on the results of different chemotherapy regimens combined with neoadjuvant irradiation and standard concomitant systemic therapies to meet the endpoint criteria of local control and pCR (Table 2).

In the most famous study, the ACCORD12 trial, the aim was to inspect the efficacy of two different CRT regimens in resectable rectal cancer patients. In order to fulfill this purpose, a 3-year follow-up was put into work. Each patient was randomly assigned to CRT with either CAP45 (45-Gy RT in combination with capecit-

abine 5 days weekly) or CAPOX50 (50-Gy RT in combination with capecitabine and oxaliplatin). This study's short-term results showed no significant differences in clinical outcomes between the two groups [19]. The clinical outcomes at 5 years of the ACCORD12 trial were also reported. Multivariate analysis showed no differences in disease-free survival (DFS) or OS between groups. In conclusion, it was announced that adding oxaliplatin to standard treatment did not improve local control, DFS, and OS in the ACCORD12 trial [20].

To achieve better long-term outcomes and better response with surgery, Lee et al. [21] compared two different concurrent chemotherapy regimens for LARC patients; capecitabine alone versus capecitabine plus irinotecan. In summary, based on pathologic and radiologic findings, no statistically significant differences were found between the two groups in short-term observation. The study also tried to compare the long-term results of the two methods by analyzing the 5-year local control rate, DFS, and OS. Again, there were not any meaningful differences between the two groups, indicating that irinotecan addition to a capecitabine does not have remarkable advantages over capecitabine alone and is not recommended as a standard treatment of choice in the clinic.

A randomized phase II study of capecitabine-based CRT with or without bevacizumab (BEV) in resectable LARC was done in an open, multicenter randomized phase II trial by Salazar et al. [22]. Patients were randomized to receive 5 weeks of RT with concurrent CAP (Arm A) or the same schedule with biweekly BEV 5 mg/kg (Arm B). The results of this study support the data described previously in single-arm studies about the practicability of adding BEV to a standard neoadjuvant capecitabine-based CRT regimen, as well as its potential role in down-staging.

A phase II trial investigated the preoperative RT with two different parallel chemotherapy regimens: (1) capecitabine (1,200 mg/m^2/daily for 5days a week) plus irinotecan (50 mg/m^2 weekly × 4); and (2) capecitabine (1,650 mg/m^2/daily for 5 days a week) plus oxaliplatin (50 mg/m^2/weekly × 5). The efficacy results for both arms were similar to other reported studies. Thus, the authors were uncertain to recommend a second agent plus capecitabine for concurrent chemotherapy, but they suggested further studies using irinotecan [23].

Bazarbashi et al. [24] studied the effect of adding weekly cetuximab to capecitabine concurrent with RT. The authors concluded that this combination was attainable with acceptable toxicity in LARC, and it was associated with better pCR compared to historical controls.

The addition of systemic therapies based on the molecular profile of tumors has been investigated in rectal cancer patients in a phase II trial by Gollins et al. [25]. In this investigation, the significance of pre-treatment and post-resection RAS mutations was evaluated through treatment with a preoperative chemotherapy regimen consisting of capecitabine, irinotecan (60 mg/m^2weekly from week 1 to 4), and cetuximab (weekly from week 0 to 5). As a result, this regimen was proved to be acceptable and met its primary R0 re-

Table 2. Concurrent chemotherapy intensification

Study, year	RT dose	Study arm	N	pCR	Toxicity	DFS	OS
Lee et al. [21], 2013	50.4 Gy	Concurrent CAP vs. CAP/irinotecan	231	28.6% vs. 37.5% (p = 0.247)	ND	5-yr RFS: 80.8% vs. 77.2%; p = 0.685	5-yr OS: 88.4% vs. 90.4%; p = 0.723
Salazar et al. [22], 2015	45 Gy	Concurrent CAP + BEV vs. CAP alone	90	16% vs. 11% (p = 0.54)	G3-4 toxicity: 16% vs. 13%	ND	ND
Wong et al. [23], 2015	50.4 Gy in 1.8-Gy fx	CAP + OX vs. CAP + IRI	104	21% vs. 10%	ND	4-yr DFS: 62% vs. 68%	4-yr OS: 75% vs. 85%
Bazarbashi et al. [24], 2016	50.4 Gy	Concurrent CAP + cetuximab	50	0.04	Cetuximab-induced skin reactions (33%), radiation-induced skin toxicity (13%) and diarrhea (20%)	4-yr DFS: 80%	4-yr OS: 93%
Gollins et al. [25], 2017	45 Gy	Single arm: Concurrent CAP + cetuximab + IRI	82	0.17	G3: 47% G4: 12%	37.4-mo PFS: 67%	37.4-mo OS: 80%
Haddad et al. [26], 2017	50–50.4 Gy	Concurrent CAP + OX vs. CAP alone	63	34% vs. 13% (p = 0.072)	G3 diarrhea: 22% vs. 0%; p = 0.006	ND	ND
ACCORD 12/0405 PRODIGE [19,20], 2012, 2017	-	Concurrent CAP + OX vs. CAP alone	598	19.2% vs. 13.9% (p = 0.09)	Acute G3-4: 25.4% vs. 10.9%; p < 0.001	5-yr DFS: 66.1% vs. 63.1%; p = 0.9	5-yr OS: 82% vs. 73%; p = 0.3

RT, radiotherapy; pCR, pathological complete response; DFS, disease-free survival; OS, overall survival; CAP, capecitabine; BEV, bevacizumab; OX, oxaliplatin; IRI, irinotecan; ND, not defined.

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section endpoint. Also, there was a non-significant enhancement in progression-free survival (PFS) and OS for RAS wild-type in comparison to anytime-mutated tumors.

A clinical trial by Haddad et al. [26] investigated the effects of adding oxaliplatin (60 mg/m^2 weekly for 5–6 cycles) to capecitabine based CRT in LARCs. This particular trial evaluated down-staging as a short-term replacement for PFS. In conclusion, this study revealed that the addition of oxaliplatin to CRT might benefit down-staging in the short term. Given that oxaliplatin is still experimental, the article suggested such a regimen might be beneficial in patients suspected of having positive circumferential resection margins in pre-treatment magnetic resonance imaging.

As seen above, augmenting the systemic part of the neoadjuvant treatment although have been feasible but conferred little benefit so far. Most authors of such trials suggested further studies with some of the agents. To sum up, the standard of care is still using fluorouracil or capecitabine plus RT as the concurrent systemic regimen.

Induction or Consolidation Systemic Therapy

Adding more chemotherapy in the pre-RT and post-RT windows is a way of intensification of neoadjuvant therapy in rectal cancer. Some RT effects are durable even after the last fraction and using systemic therapy in this time-frame would have some radio-sensitizing effects along those effects harbored by the full-dose systemic therapy itself. A good example of adding more systemic therapy before or after CRT is called total neoadjuvant therapy (TNT). In this method induction chemotherapy is usually followed by CRT with or without consolidation chemotherapy [27].

Higher toxicities are expected during TNT due to the increased intensity of the chemotherapeutic agents, but no grade 4 toxicities were reported in the included papers (Table 3). Grade 3 leukopenia was a common adverse effect in most studies, occurring in 10%–13% of the patients. Radiation dermatitis was also seen in about 6% of the cases [28-30]. However, complete clinical or pathological responses were achieved in 17% to 42% of the cases. The highest complete response rate was reported in a regimen of 50.6 pelvic RT in 22 fractions, followed by 4 cycles of CAPOX [28-30].

Spanish GCR-3, a phase II randomized trial, was designed to measure the benefits of adding chemotherapy before CRT and surgery. Patients with distal or middle third rectal cancer were randomly assigned to two different arms; preoperative CRT followed by surgery and four cycles of postoperative CAPOX or four cycles of induction CAPOX followed by CRT and surgery. In conclusion to this

Table 3. Induction or consolidation systemic therapy

Study, year	RT dose	Study arm	N	pCR	Toxicity	DFS	OS
Fernandez-Martos et al. [31], 2015	-	CRT then surgery and adjuvant CAPOX vs. induction CAPOX then CRT then surgery	108	13% vs. 14%	ND	5-yr: 64% vs. 62%; p = 0.85	5-yr: 78% vs. 75%; p = 0.64
Fernandez-Martos et al. [32], 2019	50.4 Gy	mFOLFOX6 + aflibercept vs. mFOLFOX6 alone	180	22.6% vs. 13.8% (p = 0.15)	Hypertension: 24.3% vs. 1.5% Postoperative complications: 15.5% vs. 12.9%	ND	ND
Fokas et al. [28], 2019	50.4 Gy in 28 fx	Induction FOLFOX vs. consolidation FOLFOX	311	17% vs. 25%	37% vs. 27%	ND	ND
Masi et al. [33], 2019	50.4 Gy	Single arm: induction FOLFOXIRI + BEV	49	0.364	Neutropenia: 41.6% Diarrhea: 12.5%	2-yr: 80.45%	ND
OPRA trial [35], 2020	54 Gy	Induction vs. consolidation FOLFOX or CAPOX	324	ND	ND	3-yr DFS: 78% vs. 77%; p = 0.9 3-yr MFS: 81% vs. 83%; p = 0.86	ND
Conroy et al. [36], 2020	50 Gy	CRT alone vs. induction mFOLFIRINOX then CRT	461	11.7% vs. 27.5% (p < 0.001)	ND	3-yr DFS: 68.5% vs. 75.7% 3-yr MFS: 71.7% vs. 78.8%	3-yr OS: 87.7% vs. 90.8%

RT, radiotherapy; pCR, pathological complete response; DFS, disease-free survival; OS, overall survival; CRT, chemoradiotherapy; CAPOX, capecitabine and oxaliplatin; FOLFOX, 5FU + leucovorin + oxaliplatin + irinotecan; mFOLFOX, modified FOLFOX; BEV, bevacizumab; ND, not defined.

trial, both treatment methods approached similar results. However, the group with systemic therapy before CRT and surgery showed lower acute toxicity and better overall compliance; therefore, it warranted further investigation [31].

In the Spanish GEMCAD 1402 study, adding aflibercept (4 mg/kg every 2 weeks for 6 cycles) to the induction modified FOLFOX (5FU, leucovorin, and oxaliplatin) followed by CRT and TME yielded better pCR and similar surgical complications than the induction modified FOLFOX alone [32]. These results granted to go for a phase III trial with this approach.

TNT is recognized as a new standard for rectal cancer treatment. To test this hypothesis, in CAO/ARO/AIO-12 trial, patients were divided into two arms. Arm A received induction chemotherapy using three cycles of FOLFOX before 5FU/oxaliplatin CRT (5FU 250 mg/m^2 on days 1 to 14 and 22 to 35 and a 2-hour infusion of oxaliplatin 50 mg/m^2 on days 1, 8, 22, and 29 of RT), and Arm B received consolidation chemotherapy after CRT. The induction or consolidation regimens were as follows: oxaliplatin 100 mg/m^2 + leucovorin 400 mg/m^2 + continuous 46-hour infusion of 5FU 2,400 mg/m^2, repeated on day 15 for a total of 3 cycles. It was concluded that CRT followed by consolidation chemotherapy resulted in better compliance with CRT but worse compliance with chemotherapy compared with Arm A. Only the CRT followed by chemotherapy fulfilled the predefined trial hypothesis of a 10% better pCR rate. Accordingly, this sequence was set for the baseline group for future trials on TNT [28].

As it is known, the CRT alone does not achieve the effective control of distant metastases as is expected. The addition of induction chemotherapy plus BEV in phase II single-arm trial named TRUST was examined. Patients underwent 6 cycles of induction FOLFOXIRI plus BEV, followed by CRT and BEV. The authors claimed that this strategy might be able to improve distant disease control in LARC [33].

OPRA, a phase II multi-institutional study, evaluated selective non-operative management (NOM) in LARC in those with clinical response to avoid unnecessary surgery [34]. Patients with stage II or III who were eligible for TME were randomized to receive 5FU or capecitabine-based CRT plus induction versus consolidation FOLFOX/CAPOX as two forms of TNT. Those who achieved a clinical complete or near-complete response were offered NOM while those with residual disease underwent TME. The 3-year preliminary results demonstrated that by delivering TNT, we would not just enhance the patient's quality of life but also, we would be able to shorten the time needed before ileostomy reversal. Also, it was established that avoiding surgery in patients with tumors that respond to CRT will minimize over-treatment without compromising survival. In contrast to induction chemotherapy, more patients with consolidation chemotherapy were suggested to achieve NOM [35].

Conroy et al. [36] conducted PRODIGE 23, a clinical phase III trial to validate the TNT approach in LARC prospectively. The efficacy of 6 courses of mFOLFIRINOX as induction chemotherapy followed by CRT and TME within 3 months was compared to the control group consisting of only preoperative CRT and TME. The induction regimen consisted of 6 cycles of modified FOLFIRINOX (oxaliplatin 85 mg/m^2, leucovorin 400 mg/m^2, irinotecan 180 mg/m^2 D1, and 5FU 2.4 g/m^2 over 46 hours) every 14 days. Adjuvant chemotherapy with mFOLFOX6 or capecitabine was allowed depending on the center's interest. Although the OS data has yet to be mature, the benefit of total neoadjuvant therapy on pCR, DFS, and metastasis-free survival was shown.

Several robust studies have been listed above that addressed the efficacy and safety of adding induction or consolidation systemic therapy. The most popular method in this setting is TNT that seems to become a famous paradigm in the near future. Considering this approach's relative novelty, high pCR and metastasis-free survival and DFS rates in the TNT studies made us eagerly expect the long-term results regarding the OS rates and chronic toxicities.

Conclusion

Three main approaches exist to intensify the neoadjuvant chemoradiotherapy for rectal cancer. Many investigators with various practical backgrounds have examined the efficacy and safety of intensified regimens prospectively and retrospectively. It seems that the TNT has a brighter future, considering the strength of results and power of the clinical trials. We should keep in mind that LARC has a relatively high survival rate with current therapies, and there is an availability of various agents in the advanced setting. Thus, long follow-ups are needed to see the effect of different approaches on overall survival.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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