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New standard in locally advanced rectal cancer

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Abstract

In the following review we intend to ascertain the optimal neoadjuvant therapy in patients with locally advanced rectal cancer. In 2004, a study revealed that chemoradiotherapy (CRT) resulted in better local control when performed preoperatively rather than postoperatively, thus neoadjuvant treatment was established as a standard treatment. Subsequently, the Polish study and the Trans-Tasman Radiation Oncology Group showed no statistically significant difference between concomitant CRT over 5 wk *vs* short-course radiotherapy (RT). Therefore, both were established as standard neoadjuvant treatments. Later, the Stockholm III study demonstrated that short-course RT had a higher complete pathological response than long-course RT. It also showed that a delay between RT and surgery presented fewer complications. This opened a window of time to provide an early and effective systemic treatment to prevent distant metastases. Studies show that short-course RT plus oxaliplatin-based chemotherapy could achieve this. When comparing this total neoadjuvant treatment (TNT) *vs* concomitant CRT, the former showed greater complete pathological response and lower acute toxicity. Studies presented during 2020 have also shown the benefits of TNT in terms of complete pathological response, as well as disease and metastasis-free survival. Our review suggests that probably TNT should be the new standard treatment for these patients. However, we will have to wait for the full text publications of these studies to confirm this statement.

Key Words: Locally advanced rectal cancer; Total neoadjuvant treatment; Short-course radiotherapy; Oxaliplatin; Neoadjuvant chemoradiotherapy; Long-course radiotherapy

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Core Tip: In this review we intend to ascertain the optimal neoadjuvant therapy in patients with locally advanced rectal cancer. In terms of chemotherapy (CT) it has recently been demonstrated that oxaliplatin-based CT after short-course radiotherapy results in greater pathological response and lower acute toxicity than concomitant chemoradiotherapy. Studies presented during 2020 have also shown this benefit, as well as better disease and metastasis-free survival. Our review suggests that probably total neoadjuvant treatment should be the new standard treatment for these patients. However, we will have to wait for the full text publications of these studies to confirm this statement.

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INTRODUCTION

Since the Gastrointestinal Tumor Study Group study was published in the *New England Journal of Medicine* in 1985, we have known that locally advanced rectal cancer surgery alone is not sufficient^[1]. This research demonstrated a clear benefit in the addition of radiotherapy (RT) at around 5 wk and concomitant chemotherapy (CT) after surgery (adjuvant). In Sweden, they performed preoperative or neoadjuvant RT treatment. Thus, in 1997, they published a randomized study of surgery alone *vs* RT 2500 centi-gray (cGy) delivered in 5 fractions in 1 wk (short-course RT) followed by surgery within one week. Patients who received RT had better local control and higher overall survival^[2].

Up to that date, two randomized studies existed which showed the benefit of adding treatments to surgery for both neoadjuvant short-course RT and concomitant adjuvant chemoradiotherapy (CRT). It was not clear whether it was better to carry out this treatment before or after resection. In 2004, a study performed by Sauer *et al*^[3] was published showing that CRT treatment over 5-6 wk was better when performed preoperatively in comparison to postoperatively as it resulted in better local control and was better tolerated. At this point, neoadjuvant treatment was established as the standard.

Taking this into consideration, what is the best neoadjuvant treatment? Concomitant CRT over 5 wk (dose of 5000-5040 cGy delivered in 25-28 fractions in 5-5.5 wk) *vs* short-course RT. Two randomized studies were performed on this subject, the Polish study and the TROG^[4,5] trial. Both studies showed that there was no statistically significant difference between these neoadjuvant treatments and so both were established as standard treatments.

It seems counter-intuitive that a short-course RT treatment with 2500 cGy is equivalent to a concomitant CRT treatment with double the dose. However, when analyzing this from a radiobiological perspective, these doses are equivalent as the 2500 cGy are administered in doses of 500 cGy per session *vs* the 180-200 cGy per session for concomitant CRT. In addition, the treatment is completed in only 1 wk *vs* 5-5.5 wk. In fact, the 1 wk treatment administers a dose equivalent to 3570 cGy in comparison to 3440 cGy, which is the dose administered in the long-course treatment, if one uses the linear quadratic model and factors in total treatment time^[6].

This was clinically demonstrated in the Stockholm III study, which compared long-course RT at 5 wk, without concomitant CT, *vs* short-course RT, both neoadjuvant treatments followed by surgery after 4-8 wk. Pathology study results confirmed the radiobiology calculations. The pathological complete response was better in the short-course RT group, reaching 10.4% *vs* only 2.2% in the long-course RT group^[7]. The same study compared short-course RT with and without pre-surgical delay (following week *vs* a delay of 4-8 wk) and showed that the oncological results were similar but that a delay allows for fewer surgical and post-operative complications^[8]. The authors concluded that a pre-resection delay should be made. This delay opens a window of time to provide effective systemic treatment early in the course of treatment that

prevents the development of distant metastases. This is very relevant because randomized studies consistently show an incidence of distant metastases of around 30% in patients who are treated for locally advanced rectal cancer^[9].

NEW PARADIGM

The new paradigm is to advance useful systemic treatment with oxaliplatin (OXA)-based CT in order to prevent the development of distant metastases. In this regard, the ideal is to be able to perform all adjuvant treatments preoperatively. This concept is known as total neoadjuvant treatment (TNT). The main objective of this is to prevent distant metastases by instructing the patient to use effective systemic treatment early in the course of their disease. Other benefits of TNT are improved local response that can manifest itself in improved clinical and pathological complete response, improved tolerance and adherence to treatment, and reduced total time for complete treatment with earlier ostomy resolution. In fact, this last point was demonstrated in a study presented at the American Society of Clinical Oncology (ASCO) 2019 in patients who received TNT through short-course RT and CT with OXA^[10].

In 2016, the STELLAR study was presented at the American Society of Radiation Oncology, which compared short-course RT followed by CT with OXA for 4 cycles with concomitant CRT, as neoadjuvant treatments. After surgery in both treatments, CT with OXA was recommended, 2 cycles for the short-course RT group and 6 cycles for the concomitant CRT group. The experimental group that underwent short-course RT followed by CT was superior in terms of pathological complete response, which was obtained in 25.7% of cases *vs* only 7.9% of cases in the concomitant CRT control group. There was also a difference in complete clinical response of 11.7% in the experimental group *vs* 0% in the control group^[11]. These preliminary data were updated at the European Society for Medical Oncology 2018 Congress. A benefit continued to be exhibited in pathological complete response for the short-course RT group followed by CT which turned out to be 26.2% *vs* 5.3% for the group that received concomitant CRT^[12].

In 2016, the Polish study II was published, which compared short-course RT followed by OXA-based CT *vs* concomitant OXA-based CRT in patients with fixed cT4 or cT3 cancer. In this study, 56% of patients had tumors located in the lower rectum. Overall survival at 3 years was superior in the short-course RT group with 73% *vs* 65% for the concomitant CRT group^[13]. The long-term results of this study with 7 years of follow-up showed a median overall survival of 89 mo for the short-course RT group *vs* 81 mo for the concomitant CRT group, with no statistical difference^[14]. This second publication shows that only 70% of patients in both groups received OXA because during the course of the study, other studies appeared that showed greater toxicity due to concomitant CRT with OXA. This is probably why the benefit initially shown, when most of the randomized patients had received OXA, was lost when a significant percentage of admitted patients later switched to OXA-free treatment. In this new scenario, the benefit that the short-course RT group followed by OXA-based CT has to start early effective systemic treatment during disease progression that may prevent the development of metastases is lost. In any case, this study reinforces that short-course RT is at least equivalent to concomitant CRT in locally advanced rectal cancer. It is important to note that concomitant CRT was not superior to short-course RT in any outcome, but acute toxicity was lower for short-course RT ($P = 0.006$). When treatments are equivalent in oncological outcome, we must opt for the treatment with lower toxicity, which in this case was the short-course RT.

At IRAM Clinic (Santiago, Chile), we started TNT in 2015 with short-course RT followed by 4 cycles of folinic acid/5-fluorouracil/oxaliplatin (FOLFOX) for 2 mo^[15]. To date, we have 58 patients with pathological results, where 77.5% had cT3 or cT4 cancers and 86.2% were classified as N+. A total of 82.7% of patients were classified in stages using CT scans of the chest, abdomen and pelvis and 62% with pelvic magnetic resonance imaging (MRI). Pathological complete responses were obtained in 22.4% of patients and 65.5% of patients were down staged from stage III to a lower stage (stage II, I or 0). Compared to the study performed by Sauer *et al*^[3] of concomitant CRT, they showed pathological complete response rates of 8% and downstaging of 15%.

At ASCO 2020, results were presented from the RAPIDO study that randomized patients with high-risk features for failure on MRI to undergo TNT with short-course RT followed by CT with OXA-based CT for 18 wk followed by surgery *vs* concomitant CRT followed by surgery and then 24 wk of OXA-based CT. The TNT group tolerated the treatment well with the following grade 3 or higher adverse events: Diarrhea in

17.6% of the group, vascular disorders in 8.5%, all other adverse events affected under 5%. The primary focus was treatment-related failure, which was 23.7% in the group receiving TNT *vs* 30.4% in the control group ($P = 0.019$). The pathological complete response doubled in the TNT group, reaching 28.4% *vs* 14.3% ($P < 0.001$) and distant metastases occurred in 20% of patients in the TNT group *vs* 26.8% of patients in the concomitant CRT group ($P = 0.005$). These results were found in a patient population with very high risk of recurrence with cT4 disease in 31.8%, N2 in 65.4% and a compromised mesorectal fascia in 61.7%^[16].

In addition, the PRODIGE 23 study was presented where TNT and FOLFIRINOX was randomized for 3 mo, followed by concomitant CRT, then total mesorectal excision (TME) and then CT with FOLFOX or capecitabine for 3 mo *vs* a control group with concomitant CRT followed by TME and then CT with adjuvant FOLFOX or capecitabine for 6 mo^[17]. It is important to note that in the pre-operative re-staging, 4.7% of control group patients became metastatic *vs* 1% of those in the experimental group ($P = 0.03$). This reinforces the fact that the classical approach of starting treatment with concomitant CRT does not prevent the development of distant diseases and that is why we must stop treating patients in this way and shift the paradigm towards TNT. The grade 3 or higher adverse events in adjuvant treatment alone were 44.4% for the TNT group. This seems a little high considering that these data do not consider the adverse effects of other stages of treatment (neoadjuvant) and that only 70.6% were able to receive adjuvant treatment and, of these, only 80.4% completed all cycles. This is equivalent to only 56.7% of patients randomized to TNT. However, TNT resulted in better disease-free survival at 3 years with 75.7% *vs* 68.5% ($P = 0.034$) and better metastasis-free survival at 3 years with 78.8% *vs* 71.7% ($P = 0.017$).

Another study presented at ASCO 2020 was the Organ Preservation of Rectal Adenocarcinoma (OPRA) study^[18]. Patients with rectal cancer with a better prognosis than in the RAPIDO and PRODIGE 23 studies with stage II or III were randomized to concomitant CRT and then OXA-based CT for 4 mo *vs* OXA-based CT for 4 mo and then concomitant CRT. Patients were then re-staged and, if they achieved a clinical response, they entered an active follow-up protocol. Those who had no response went on to TME. With a median follow-up of 2.2 years, surgery-free survival at 3 years was better for the group that started with RT ($P = 0.007$). Grade 3 or higher toxicity occurred in 45.5%-49% of patients. The author concluded that further follow-up is required but that organ preservation in rectal adenocarcinoma could be a safe alternative in some patients.

CONCLUSION

Considering both the historical and recent evidence, probably the new standard treatment for locally advanced rectal cancer will be TNT as it shows better results than concomitant CRT in at least 2 randomized studies. However, we will have to wait for the full text publications to confirm this statement. Among the TNT options, the best alternative is short-course RT followed by OXA-based CT for 18 wk following the RAPIDO study protocol, since it achieves similar metastasis-free survival rates at 3 years as PRODIGE 23 (80% RAPIDO *vs* 78.8% PRODIGE 23), despite the fact that the included patients had a worse prognosis since cT4 disease was 31.8% in RAPIDO *vs* 17.8% in PRODIGE 23 and a greater risk of a positive lateral margin (compromise of mesorectal fascia in 61.7% in RAPIDO *vs* predicted lateral margin < 1 mm 26% in PRODIGE 23) with a toxicity profile that seems to be lower (Table 1). The OPRA study is not comparable because it included patients with a much better prognosis (T1-2 13%, N0 28% in the best group) and still has little follow-up (2.2 years), but suggests that we need to start with RT and then follow with OXA-based CT, and not the other way round.

Table 1 Comparison between Sauer's, PRODIGE 23 and RAPIDO study

	T4	N+	Predicted lateral margin < 1 mm	Pathologic complete response	Metastasis-free survival
Sauer (%)	6	54		8	70.2
PRODIGE 23 (%)	17.8	89.1	26	27.8	78.8
RAPIDO	31.8	90	61.7	28.4	80

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