Rectal Cancer

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Locally advanced rectal cancer represents a major health problem. Recently, the important results obtained with RAPIDO and PRODIGE 23 trials have changed the treatment algorithm of this disease.

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1. Background

Rectal cancer accounts for around 35% of total colorectal cancer, and constitutes a major health concern. The outcome for patients with rectal cancer has significantly improved in the last thirty years. Previously, surgery was not standardized and local relapses in the pelvic area occurred in more than one third of all patients with apparently localized tumors. The introduction and global implementation of total mesorectal excision (TME) was the first step in improving local control by reducing local relapses to less than 5%. Preoperative radiation, which involves either a short course (SCRT) given for five days or a long course administered for five weeks with concurrent administration of chemotherapy, was a second important step in reducing local relapses to a minimum, even in locally advanced tumors, in which a clean surgical resection was not possible or would not have been curative. Locoregional staging with magnetic resonance imaging (MRI) is very useful for the proper selection of patients for preoperative treatment. Nowadays, we know that preoperative chemotherapy also provides better control of systemic relapses in those patients presenting high-risk features in whom metastatic progression is frequently observed. Moreover, surgery can be avoided in those patients that present a pathological complete response (pCR). The complete disappearance of all tumor cells in the surgical specimen has been observed in around 12% of patients after conventional preoperative chemoradiation (CRT) and up to 25% in patients receiving neoadjuvant chemotherapy as part of the total neoadjuvant treatment (TNT) strategy. These observations mean that surgery can be avoided in a higher proportion of cases, making the watch and wait approach more common, safe and curative.

According to current clinical practice guidelines, localized rectal cancer treatment relies on accurate staging procedures, which is highly dependent on pelvic magnetic resonance imaging [1]. This allows the categorization of patients according to clinically defined risk categories. Each risk category may benefit from a specific type of treatment, for example, very early low grade cT1N0 can be treated with local excision, early stages are treated with upfront surgery, namely, total mesorectal excision [2] and low to intermediate risk patients benefit from preoperative treatment, which includes either short-course radiotherapy or conventional chemoradiotherapy based on fluoropyrimidines followed by TME [3].

Patients with locally advanced rectal cancer (LARC) may have at least one of the following MRI-defined high-risk features: T3 invading 5 mm or more, particularly those that involve or reach less than 1 mm of the mesorectal fascia, T4, extra-mural vascular invasion (EMVI), N2 and extra-mesorectal nodal involvement. Distant metastases are more frequently seen during patient follow up when these features are present. In these patients, systemic relapses are significantly more frequent. Conventionally, they have been treated with preoperative CRT followed by surgery and in some cases, adjuvant chemotherapy according to the guidelines. However, the recently published RAPIDO and PRODIGE 23 trials have brought neoadjuvant chemotherapy to the fore as a new standard of care.

2. Total Neoadjuvant Treatment as a New Standard of Care for LARC (Locally Advanced Rectal Cancer)

The use of neoadjuvant chemotherapy in the treatment of LARC was recently revolutionized at the ASCO 2020 virtual meeting when the results of two pivotal randomized phase 3 trials, the RAPIDO [4] and the PRODIGE 23 [5] trials were presented. Both studies deal with TNT in LARC patients and establish a new standard of care. However, they have several differences, which are further discussed below and are described in Table 1 and Table 2.

Table 1. Comparison of the patient characteristics in the RAPIDO [4] and PRODIGE 23 [5] trials.

Patient Characteristics	RAPIDO (TNT vs. CRT)	PRODIGE 23 (TNT vs. CRT)
Median age	61 yrs vs. 61 yrs	61 yrs vs. 62 yrs
Patients enrolled	462 vs. 450	231 vs. 230
cT4 (%)	30.4% vs. 31.8%	17.8% vs. 15.6%
cN2 (%)	68% vs. 68%	Not stated
EMVI+ (%)	32% vs. 28%	Not stated
MRF involved	62% vs. 60%	26% vs. 27.7%

CRT: chemoradiotherapy; TNT: total neoadjuvant chemotherapy; EMVI: extramural vascular invasion; MRF: mesorectal fascia; yrs: years.

Table 2. Comparison of the outcomes of the RAPIDO [4]and PRODIGE 23 [5] trials.

Outcomes	RAPIDO (TNT vs. CRT)	PRODIGE 23 (TNT vs. CRT)
Median FU	4.6 yrs	3.8 yrs
Primary endpoint	3-yrs DrTF 23.7% vs. 30.4% (HR 0.75 [95% CI 0.60–0.96]; *p* = 0.019)	3-yrs DFS 75.7% vs. 68.5% (HR 0.69 95% [CI 0.49–0.97]; *p* = 0.034)
3-year MFS	80% vs. 73.2%	78.8% vs. 71.7%
pCR rate	28.4% vs. 14.3%	27.5% vs. 11.7%
Local relapse	8.7% vs. 5.4%	4.8% vs. 7%
3-year OS	89.1% vs. 88.8%	90.8% vs. 87.7%

FU: follow up; CRT: chemoradiotherapy; DrTF: disease-related treatment failure; DFS: disease-free survival; TNT: total neoadjuvant chemotherapy; pCR: pathological complete response; OS: overall survival; yrs: years.

An important phase 3 study, the Stockholm III trial, demonstrated that surgery can be safely delayed after SCRT for up to 12 weeks, and that this approach leads to an increased pCR rate without affecting postoperative complications [6][7]. Other studies have also examined the possibility of exploiting this window to administer systemic treatment, and ultimately, to move the regimen administered in the adjuvant setting to the preoperative one [8][9]. This approach was also used in the RAPIDO trial.

Interestingly, the Dutch M1 trial demonstrated that in patients with stage IV rectal cancer, administering SCRT on the primary tumor followed by FOLFOX-bevacizumab chemotherapy and then surgery after 6–8 weeks resulted in downstaging the primary tumor in 47% of patients with a 26% pCR rate in the primary tumor [10], and almost one third of patients were alive after a median follow up of more than 8 years [11].

The patient population in the RAPIDO trial consisted of those with MRI-defined high-risk locally advanced disease including cT4a/b, extramural vascular invasion, cN2, involved mesorectal fascia or enlarged lateral lymph nodes considered to be infiltrated. It is important to note that pelvic MRI was mandatory. Patients randomized to the experimental arm received SCRT followed by six cycles of CAPOX or nine cycles of FOLFOX followed by TME. Patients in the control arm received standard CRT followed by TME 8–10 weeks after CRT completion. Adjuvant chemotherapy was allowed depending on the investigator’s criteria.

When the trial commenced, the primary endpoint was DFS but in 2016 this was amended to time to disease-related treatment failure (tDrTF), which included locoregional failure, distant metastasis, new primary colorectal tumor or treatment-related death. Later, in 2017, a change was also made to the statistical hypothesis due to the low event rate at the second planned interim analysis. Between 2011 and 2016, 920 patients were included. The study met its primary endpoint, showing a statistically significant benefit in tDrTF at 3 years with an HR of 0.75. The 3-year DrTF rate was lower in the experimental arm (23.7% vs. 30.4%), as was the 3-year distant metastasis rate (20% vs. 26.8%). The local relapse

rate difference was not statistically significant between the two arms: 8.3% in the experimental vs. 6% in the standard arm (p = 0.12). This occurred despite the higher quality of mesorectal surgery in the standard arm compared to the experimental arm (85% vs. 78% intact mesorectal plane, respectively, p = 0.032) [12]. Also, 92.2% of patients allocated to the experimental group underwent curative surgery vs. 88.9% in the control arm (p = 0.086), an important finding considering the population of the trial, which had a high local disease burden.

As regards pathological response, it is noteworthy that 28.4% of patients in the experimental group achieved pCR compared to 14.3% in the control arm. As expected, higher toxicity was detected in the experimental arm, due to the intensive treatment. Moreover, a high compliance to systemic treatment was achieved with the experimental schedule of SCRT followed by preoperative systemic chemotherapy with FOLFOX or XELOX. At the time of reporting, the 3-year OS rate was not significantly different between the two arms, but the number of events is too low (less than 18% of patients deceased in both arms) to assess OS as a secondary endpoint at this time.

The PRODIGE 23 trial investigated an even more intensified regimen, which consisted of triplet mFOLFIRINOX chemotherapy (5-fluorouracil, irinotecan and oxaliplatin) added to standard CRT. The target population was patients with either stage II or III rectal cancer, thus patients without MRI high-risk features were also included. As in RAPIDO, pelvic MRI was mandatory in this study. The standard arm consisted of preoperative CRT followed by surgery and then adjuvant chemotherapy. The experimental arm consisted of six courses of mFOLFIRINOX followed by standard CRT, surgery and adjuvant chemotherapy. The choice of adjuvant treatment was mFOLFOX or capecitabine and was left to the center's discretion. The primary endpoint of this trial was 3-yr DFS.

Between 2012 and 2017, 461 patients were included in this study, which also met its primary endpoint, and showed an increase in 3-year DFS in favor of the experimental arm: 75.7% vs. 68.5% (HR 0.69). Three-year metastasis-free survival was higher in the triplet chemotherapy group (78.8% vs. 71.7%). The experimental arm almost tripled the rate of pCR (27.5% vs. 11.7%) compared to standard CRT. Survival data are not yet available. Overall, the authors report that despite the complexity of the treatment it was well tolerated, and patients were able to complete it. Indeed, authors did not observe significant differences in quality of life scores between the treatment arms [13].

Both the RAPIDO and PRODIGE 23 trials demonstrate a clinically relevant and statistically significant decrease in relapses as well as an increase in pCR. Although important, the quantitative effect observed is moderate. Nonetheless, if the ESMO Magnitude of the Clinical Benefit Scale for potentially curative therapies was applied both trials would score as A, because they show an improvement in DFS or DrTF alone (primary endpoint) with the lower limit at the 95% confidence interval HR below 0.65 without mature survival data [14]. However, the intensity of both neoadjuvant chemotherapy schedules would certainly limit their use in elderly patients. In fact, the median age of participants was 62 years in both studies and only 11% of the patients in the PRODIGE 23 trial were over 70.

Although the two trials have several similarities, they have key differences that shape their different responses to clinical questions (Table 1). It is evident that RAPIDO was far more selective in its inclusion criteria, and around 40% of patients received no adjuvant treatment, as per hospital policy, while in the PRODIGE 23 trial it was part of the treatment protocol. Therefore it could be argued that a subset of patients in PRODIGE might have been overtreated, while it is unclear from the study whether there is a subpopulation that really benefits from intensified treatment. In contrast, due to its straightforward and stringent MRI-defined high-risk selection criteria, the RAPIDO trial addresses a target population with very poor prognosis for whom current treatments might be insufficient.

3. Conclusion

Neoadjuvant chemotherapy with CAPOX or FOLFOX added after short-course radiation and delayed surgery or upfront mFOLFIRINOX before long-course chemoradiation followed by surgery are two validated options to treat LARC with MRI-defined high-risk features. Both approaches have been validated in randomized phase III studies showing clinically relevant and statistically significant reduction in disease-related treatment failure or disease-free survival. Moreover, fewer metastatic relapses and more pCRs were observed. In summary, total neoadjuvant treatment has arrived as a new standard of care. Since the 2004 publication by Sauer et al. in New England Journal of Medicine [15] confirming the value of preoperative chemoradiation in reducing local relapses versus the conventional postoperative approach, these are the first trials until now showing a favorable effect in reducing the risk of systemic relapses so this becomes a new standard of care.

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