



Total neoadjuvant treatment in locally advanced rectal cancer

Francesca De Felice^{a,*}, Vincenzo Tombolini^a, Enrico Cortesi^b

^a Department of Radiotherapy, Policlinico Umberto I, "Sapienza" University of Rome, Viale Regina Elena 326, 00161 Rome, Italy

^b Medical Oncology Department, Policlinico Umberto I, "Sapienza" University of Rome, Italy

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ABSTRACT

Locally advanced rectal cancer requires a multidisciplinary management, traditionally based on neo-adjuvant (chemo) radiotherapy, conservative surgery with total mesorectal excision and adjuvant chemotherapy. Despite effective in term of local control, this strategy is linked to a high risk of distant metastasis (up to 30%). In this context, recent published randomized phase III clinical trials have tested the potential benefits with a different sequencing and/or intensification of the standard components of the trimodal therapy.

Here, we briefly assess the efficacy and discuss the clinical relevance of total neoadjuvant treatment with a focus on indications and results in the short-course radiotherapy followed by chemotherapy use for this setting of patients. Long term results and additional prospective studies are necessary to more accurately estimate the clinical benefit and further establish the role of total neoadjuvant therapy in locally advanced rectal cancer disease.

Converging clinical evidence suggests that locally advanced rectal cancer has a higher propensity to distant metastasis after standard multimodal treatment (chemoradiotherapy or short-course radiotherapy followed by surgery and adjuvant chemotherapy) implying that the use of total neoadjuvant sequences would improve survival outcomes in patients with rectal cancer [1].

In this context, short-course radiotherapy followed by chemotherapy and delayed surgery represent a potential treatment opportunity [2]. In the phase III RAPIDO trial, 920 patients with high-risk rectal adenocarcinoma (cT4 or cN2 or extramural vascular invasion or involved mesorectal fascia, or enlarged lateral lymph nodes) were randomly assigned to either standard treatment (based on neoadjuvant chemoradiotherapy) or experimental total neoadjuvant treatment (received short-course radiotherapy followed by chemotherapy and surgery) [2]. After two protocol amendments, primary clinical end-point was 3-year disease-related treatment failure (DrTF), defined as loco-regional failure, distant metastasis, a new primary colon tumor or treatment-related death. At 3 years, the cumulative probability of DrTF was 23.7% (95% CI 19.8–27.6) in the experimental group compared with 30.4% (95% CI 26.1–34.6) in the standard treatment group (HR 0.75, 95% CI 0.60–0.95; $p = 0.019$). The RAPIDO sequence was associated with increased pathological complete responses (28% versus 14%) but higher toxicity during preoperative treatment (48% versus 25%). Overall, 368 (86.4%) of 426 patients in the experimental group and 349 (87.3%) of 400 patients in the standard of care group had surgical resection with definitive stoma [3].

Two main crucial aspects of this trial should be pointed out.

First, the choice of primary endpoint, resulting in difficulty of both data interpretation and critical comparison. Actually, for phase III trials, disease-free survival – defined as the time from randomization to local or distant recurrence, second primary other cancer, or death from any cause, including same/other cancer and non-cancer-related death – constitutes the most suitable primary clinical endpoint [4]. Adopting DrTF as primary endpoint (thus limiting clinical outcome measure only to loco-regional failure, distant metastasis, new primary colon tumor and treatment-related death), a lower proportion of events was recorded. It could probably have an important effect on the effect estimation confidence and would probably preclude direct estimation comparison with other randomized clinical trials.

Second, short-course radiotherapy was delivered to high-risk patients. According to international guidelines, it appears that short-course radiotherapy should not be prescribed in T3 any N with involved circumferential margin and T4 any N cases, because of its limited effect on improvement of resectability, preservation of sphincter function (in low located tumors) and avoidance of stoma [5,6]. By contrast, and surprisingly, in the RAPIDO trial, patients irradiated with long-course schedule had a similar frequency of no-sphincter-sparing surgery.

Despite these specific aspects of endpoint definition and treatment delivery, the results of the RAPIDO trial are important to the oncology community. Findings of the RAPIDO trial showed that total neoadjuvant treatment can be considered as a new standard of care in high-risk locally advanced rectal cancer.

For sure, the choice of optimal total neoadjuvant sequence, as well as chemotherapy regimen and radiotherapy schedule remains challenging.

* Corresponding author.

E-mail address: fradefelice@hotmail.it (F. De Felice).

Although a decreased probability of DrTF in individual patients receiving the experimental RAPIDO treatment, the other total neoadjuvant strategies designed to improve distant control might not be underestimated.

For instance, we addressed the addition of targeted agents based on K Ras mutational status (such as bevacizumab, or panitumumab/cetuximab) to the induction chemotherapy regimen and the addition of oxaliplatin to the neoadjuvant 5-fluoruracil-based chemoradiotherapy before surgery [7]. Preliminary results are encouraging and provide new input to a personalized medicine and patient-centered care model. Our intensified total neoadjuvant therapy is an example of an additional source of heterogeneity, reflecting the fact that there is currently no clear standard treatment in this clinical situation.

In brief, we agree that short-course radiotherapy followed by chemotherapy before surgery should be considered as one of the standards of care for high-risk locally advanced rectal cancer patients, especially in the COVID-19 pandemic situation [2]. But its role is not fully answered and needs to be adequately clarified. Direct comparisons remain the reference to obtain level-one evidence.

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