



## Patient-reported outcomes in PROSPECT trial (Alliance N1048) – FOLFOX is not a panacea

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The PROSPECT was a randomized phase III trial that included patients with resectable rectal cancer (clinical stage cT2-3N+ or cT3N0). The trial aimed to test the hypothesis that pre-operative chemotherapy consisting of 6 cycles of FOLFOX given over a 12-week period, followed by total mesorectal excision (TME) surgery, was non-inferior to pre-operative long-course chemoradiotherapy (CRT). The primary endpoint of the study was disease-free survival (DFS), and patients were also monitored for other relevant oncological outcomes such and health-related quality of life (HRQoL) using patient-reported outcome (PRO) tools [1,2].

We congratulate the investigators for their success in enrolling 1194 patients into a non-inferiority designed trial and applaud their use of PRO-CTCAE tools. However, we have a number of concerns regarding the interpretation of the data and how they pertain to toxicity in this patient group, which are important to clarify in the academic literature.

Firstly, we would like to stress that this trial does not represent a patient population with truly locally advanced disease by international standards. Notably, the trial excluded any patients with cT4 or cN2, or disease within 3 mm of the mesorectal fascia. The cT3 and nodal subgroups were not reported in line with international consensus, and it is concerning that just over 15% of patients were not staged with MRI. According to the ESMO rectal cancer guidelines, widely used internationally, this population would constitute early and intermediate disease in most cases [3]. Whilst circa 90% of both arms had patients with cT3 disease only 14.2% of the FOLFOX arm and 16.6% of the CRT had tumors within 5 cm of anal verge. This suggests that many of these patients could have been managed with total mesorectal excision (TME) and a preserved sphincter. Within this disease spectrum, PROSPECT supports FOLFOX as non-inferior to CRT in preventing local recurrence, but given the very low local recurrence risk, neither may be necessary and thus be considered as overtreatment with accompanying toxicity.

The FOLFOX arm was also non-inferior to CRT for both DFS and OS at 5 years, underlining that neoadjuvant chemotherapy did not improve disease relapse (distant or local) [1], but the question whether neoadjuvant FOLFOX could replace adjuvant chemotherapy cannot be

answered, given that there was a high level of postoperative chemotherapy in both arms. Postoperative FOLFOX was associated with higher toxicity when patients had neoadjuvant CRT (32.6%) than neoadjuvant FOLFOX (25.6%). The use of adjuvant chemotherapy after CRT is in itself questionable with established poor compliance, increased toxicity and importantly, no Level 1 data that it increases survival [4].

The more pertinent question is whether neoadjuvant FOLFOX has a role in a risk stratified group. The ongoing ACO/ARO/AIO-18.2 phase III trial (ClinicalTrials.gov Identifier: NCT04495088) is comparing primary TME followed by stage-based adjuvant chemotherapy (only in pT4 or pN+) vs neoadjuvant FOLFOX/CapOx chemotherapy over 3 months followed by TME with inclusion criteria that are largely overlapping with those of the PROSPECT. The primary objective of this study is to demonstrate superiority for DFS.

It is questionable whether PROSPECT can really be viewed as a de-escalation strategy. Severe ( $\geq$ grade 3) acute toxicity with FOLFOX was double (41%) that of CRT (22.8%). Across 14 PRO domains, CRT was significantly superior to FOLFOX in 12 and worse in only one, diarrhoea [2]. Therefore, both clinicians and patients reported that CRT is the better tolerated neoadjuvant treatment choice.

Despite the median follow-up of 58 months, data on long-term toxicity and quality of life are still awaited. Furthermore, PRO on sexual function 1 year after TME in the CRT arm were based on 34/173 patients (20%) and 97/370 patients (26%), respectively, which should be considered when interpreting these data. We do not underestimate the late effects of pelvic CRT, and its potential for severe consequences in some patients. At 18 months, patients receiving CRT reported higher rates of fatigue, neuropathy and sexual dysfunction without a difference in HRQoL [2]. These are important data for practising oncologists where patients are managed with multimodal treatment. Advances in radiation delivery using intensity modulated radiotherapy (IMRT) can minimise doses to organs at risk and spare some long-term late effects [5,6]. More importantly, the management of rectal cancer has now shifted towards organ preservation for selected patients with clinical complete response that can limit some of the side effects from multimodal treatment [7,8].

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The true value of PROSPECT is that it adds to, rather than replaces, the therapeutic options for rectal cancer. These data will inform a multidisciplinary, patient centred discussion of evidence-based options, some of whom will undoubtedly benefit from this approach, but not everyone. We urge caution not to extrapolate these findings to patients with high-risk or low-lying rectal cancer. The colorectal research community needs to better understand the biology and derive predictive biomarkers [9] that will optimise individualised treatment solutions.

#### Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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