Adjuvant chemotherapy for rectal cancer after preoperative radiation or chemoradiation: One size does not fit all

The PROCTOR-SCRIPT trial carried out by the Dutch Colorectal Cancer Group together with Swedish investigators and published in *Annals of Oncology* in this issue [1] is yet another trial that has failed to demonstrate a significant benefit in terms of disease-free survival, recurrence rates or overall survival (OS) for adjuvant chemotherapy after preoperative chemoradiotherapy (CRT) and total mesorectal excision (TME) surgery in ypTNM stage II and III rectal cancer patients. Locally advanced rectal cancer (LARC) is associated with a high risk of local and distant recurrence. Neoadjuvant long-course (CRT) or short-course preoperative radiotherapy (SCPRT) followed by TME has become the standard of care for such patients. Currently, European and National Comprehensive Cancer Network Guidelines, recommend oxaliplatin-based chemotherapy regimen as postoperative adjuvant chemotherapy in patients with ypTNM stage III or other adverse histological features following CRT and surgery. However, the validity of this latter approach remains controversial.

This year is proving a vintage year for adjuvant chemotherapy trials in rectal cancer. PROCTOR-SCRIPT is the fourth randomised trial to be published in the last 12 months to throw light on this subject. We also have available a long-term update of a landmark trial (EORTC 22921) with definitive results [2].

PROCTOR-SCRIPT is a randomised, controlled, phase III trial, which aimed to examine the role of postoperative adjuvant chemotherapy following SCPRT or CRT. Patients were stratified according to centre, residual tumour (R0/R1), time between last irradiation and surgery, and type of preoperative treatment. To aid compliance, fluoropyrimidine monotherapy was used as adjuvant chemotherapy rather than combination chemotherapy with oxaliplatin and compared with observation only as control. The PROCTOR part of this trial started in 2000. The trial was later amended to change adjuvant chemotherapy from 5-fluorouracil/leucovorin (FU/LV) to capecitabine (SCRIPT), and eligibility extended so patients could receive preoperative CRT or SCPRT (SCRIPT) instead of radiotherapy only (PROCTOR). Patients were randomised after surgery according to postoperative findings, i.e. ypTNM stage II or III, and not according to preoperative clinical stage on imaging.

what is the available evidence?

A Cochrane meta-analysis [3] has shown a significant benefit in terms of disease-free survival (DFS) [hazard ratio (HR) = 0.75, 95% confidence interval (CI) 0.68–0.83] and OS (HR = 0.83, CI 0.76–0.91) for patients with rectal cancer who received postoperative chemotherapy (using fluoropyrimidine-based chemotherapy alone with no oxaliplatin, irinotecan or biological agents) when compared with those undergoing observation alone. Yet very few of the included studies included patients who had received preoperative radiotherapy or CRT.

As stated above, other additional but underpowered studies have recently been published. Two trials showed that, after preoperative CRT, the addition of adjuvant chemotherapy compared with control failed to improve OS and DFS and had no impact on the distant metastasis rate [4, 5]. A third small phase II randomised trial showed that the addition of oxaliplatin with adjuvant FOLFOX improves disease-free survival compared with fluorouracil plus leucovorin [6].

patients with rectal cancer who have residual nodal disease (stage III) following CRT have in the past been thought to fare very badly and even potentially be chemoresistant: so why have such patients fared better than expected in all the studies published in 2014?

Trials in the adjuvant setting in rectal cancer are notoriously difficult to perform. The problem that investigators have when a trial takes a very long time to accrue (in this case 13 years) is that the world changes around us. The statistical hypothesis becomes outdated. The estimated actuarial 5-year survival for this trial at outset was 60% in the control arm and 70% for the adjuvant chemotherapy arm. Because of advances in imaging, surgical techniques and selection, this estimation became inappropriate. The later use of capecitabine [7] may also have marginally improved outcomes over the original 5-FU/LV trials [8, 9]. In reality, the results show a 5-year survival for both arms of around 80%. Another important point is how patients are selected for trials. MRI is a very accurate tool to select high-risk rectal cancer patients for more intensive treatment approaches...
what are the strengths and weaknesses of the trial?

The strengths of the study relate to good quality TME surgery, demonstrating an intact mesorectum, no deep defects, no coning, and a smooth CRM, which was carried out in 82.7% (PROCTOR) and 66.0% (SCRIPT) of the patients. This in itself may account for better outcomes as population studies have shown an improvement in survival mirroring the performance of TME.

In contrast to other earlier European studies, compliance to adjuvant chemotherapy was good — 73.6% completed all adjuvant chemotherapy cycles and <5% failed to start. The compliance rate was 43% in the EORTC 22921 trial, 48% in the CHRONICLE trial, and 55% received three to six cycles of adjuvant chemotherapy in the Italian trial [5]. The superior chemotherapy compliance may be explained by the strategy of randomising patients postoperatively with the requirement to be fit to undergo chemotherapy 6 weeks following surgery.

The weaknesses lie in the fact that subgroups were not predefined in the study protocol, because the trial was not powered on subgroup analyses. Hence, there is no subgroup analysis for ypT and ypN stage, which has always been an area of discussion [2,11].

Based on results of a meta-analysis in colon cancer [12], adjuvant chemotherapy should start as soon as possible following surgery; otherwise, the efficacy at preventing recurrence is diminished. Chemotherapy may even be ineffective if delayed beyond 3 months. The interval from surgery to the start of adjuvant chemotherapy was recommended to be 6 weeks, but no data are provided on the median time in days/weeks from surgery to the start of chemotherapy—again there could have been an imbalance in the arms.

Following CRT longer intervals extending to 12–15 weeks appear to offer more downstaging [13] and an increased chance of achieving a pathological complete remission. Outcomes may also improve with lower 3-year local recurrence rates (1.2% versus 10.5%, P = 0.04) [14].

Also, in the CHRONICLE trial [4] by excluding patients with excessively poor prognostic features such as a ≤ 1 mm circumferential resection margin, more favourable outcomes than expected were observed. In the PROCTOR-SCRIPT trial, only 5% of patients had an R1 resection (defined as both microscopic residual tumour, as well as a circumferential resection margin of ≤ 1 mm). Hence, this is a group of patients with more favourable outcomes because it is likely that either the CRM was not initially threatened or they achieved downstaging. This factor might also partly explain the paucity of relevant events such as the low local recurrence rate.

The relatively small sample size (473) in the context of 52 recruiting centres, recruited over 13 years, may have made it difficult to match for all individual prognostic factors. Although patients were reasonably well balanced in terms of yp stage II and III in each group, there are no data provided on the finding of extramural vascular invasion; hence, there could also have been an imbalance here between the arms.

There is also no information on use of medications available to patients over-the-counter, such as aspirin and NSAIDs, which have been shown to reduce the risk of recurrence of CRC and could have influenced the risk of recurrence. In the present trial, only 15% of patients received preoperative CRT. The outcomes for patients with both downstaging and persistently involved mesorectal lymph nodes (ypN+) after SCPRT may be different from the outcomes after CRT [14–16].

Different follow-up schedules are used in the Netherlands and Sweden, which could have influenced disease-free survival and recurrence rates. Dutch patients were assessed every 3 months for the first 2 years and annually thereafter. Swedish patients were assessed 1 and 3 years after surgery or every 6 months for 3 years if recruited to the COLOFOL trial.

Hence, there is incomplete histopathological data, and some additional potential for diversity in both the population enrolled, with some receiving radiotherapy and some CRT, the interval to surgery, the chemotherapy regimen received and the follow-up protocols.

so why is it so difficult to perform and recruit sufficiently powered trials in this setting?

Both patients and clinicians appear to have strong preferences/biases for either observation or adjuvant chemotherapy in this setting. This loss of equipoise adversely impacts on accrual rates [4].

does this study change current practice?

This is a further trial, which does not support the current practice, recommended in many guidelines of administering adjuvant fluoropyrimidine chemotherapy after SCPRT or CRT. Absence of evidence does not prove lack of efficacy, but certainly suggests that adjuvant chemotherapy simply does not provide the level of benefit observed in colon cancer—or at least it is implausible that it is of benefit for the selected population in this study. Three other trials in 2014 come to the same conclusion. On the other hand, some other recently presented trials justify the use of oxaliplatin-based postoperative chemotherapy in patients with positive nodes after CRT [6] or even in all LARC patients with high-risk features defined by MRI [17].

so where do we go from here?

A meta-analysis based on individual patient data of all the recent trials comparing fluoropyrimidine-based adjuvant chemotherapy versus control, (many of which are also underpowered) reinforces these findings [18]. Only the subgroup of patients with rectal tumours located from 10 to 15 cm of the
anal verge seems to benefit from adjuvant chemotherapy. Judged by our inability to produce convincing trials and the current-based guidelines [19], a control arm of observation alone against chemotherapy is no longer feasible and a definitive answer will probably never be available. Clearly, novel initiatives and new treatment strategies incorporating neoadjuvant chemotherapy in patients with MRI-defined high-risk features should be investigated. The currently accruing RAPIDO trial, in which patients allocated to the experimental arm do receive upfront six courses of capecitabine and oxaliplatin immediately after SCPRT and before TME surgery, is a good example of this innovative concept.

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