Interpreting the RAPIDO trial

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Interpreting the RAPIDO trial: factors to consider

Authors' reply

We thank Rob Glynne-Jones, Naveena Kumar, Jonathan Yuval and colleagues, and Alessandro Pastorino and colleagues for their interest in the RAPIDO trial.[1] We agree that statistical amendments in an ongoing trial are not preferred. However, we do not agree with the confronting statement of Yuval and colleagues that "without thorough reasoning for the change in the study hypothesis, the reader is left with the impression that the changes were made to fit the already known trial results". In the statistical analysis section, we clarify the reason for changing the endpoint.[1] Obviously, no information on treatment assignment was available during this process. Furthermore, all changes were approved by the independent data safety monitoring board and medical ethics committees. For completeness, disease-free survival results were included in the appendix, showing similar results to those for disease-related treatment failure.

A planned interim analysis indicated that the required number of events would not be reached, because disease-related treatment failure events would reach a plateau. By contrast, with disease-free survival and infinite follow-up, all patients would eventually experience an event. We therefore lowered the anticipated difference in events from 10% to 7·5% but maintained the same hazard ratio, with a lower power (80%).

We acknowledge that disease-related treatment failure is a new, not yet validated surrogate endpoint for overall survival. However, almost no rectal cancer trials have reported improved overall survival, with the exception of the Swedish Rectal Cancer Trial, in which a gain of 10% in 5-year overall survival was accomplished with short-course radiotherapy after an absolute difference in local recurrence rates of 16%.[2] An absolute difference of 7% in distant metastases, as seen in RAPIDO, would require a much larger sample size and longer follow-up to detect a difference in overall survival. However, we consider this reduction in metastases to be an important step towards reducing mortality in rectal cancer.

Despite the suggestion of Yuval and colleagues to evaluate adverse events on an intention-to-treat basis, we believe that the more commonly used as-treated basis provides more information.

Glynne-Jones and Pastorino and colleagues express concern about the increased locoregional failure rate in the experimental group of the trial. However, drawing conclusions from non-significant findings should be done with extreme care. The Polish II trial (including fixed cT3 and cT4 tumours and comparing standard chemoradiotherapy with short-course radiotherapy followed by three cycles of FOLFOX4) did not find a difference in the cumulative incidence of local failures at 10 years.[3] The statement that short-course radiotherapy is a suboptimal radiotherapy regime is not justified. Also, the concern of Kumar regarding cT4 tumours is not supported by the Polish II trial results.

A prolonged interval between conclusion of radiotherapy and surgery is beneficial for patients with tumours responding to neoadjuvant therapy, because it provides the opportunity for tumour downsizing or downstaging, or even a complete response. However, a subset of patients are poor responders, or even non-responders, at risk of disease progression during treatment. Irrespective of the type of preoperative treatment, patients progressing during neoadjuvant treatment are more likely to have ypT4 tumours and are at risk of non-radical resections. A high pathological complete response rate could therefore not be directly associated with the R0 rate, as suggested by Kumar. Only a very small proportion of patients showed tumour progression before surgery in either treatment group. MRI after three cycles of CAPOX, as was done at some centres, might identify poor responders and prevent disease progression if surgery is brought forward.

We understand the need for further information on histological tumour regression, but this was not a secondary endpoint (section 6.5.2 of the protocol merely describes regression grading) and analyses are planned after central review of the pathology.

Lastly, Pastorino and colleagues question whether the standard of care group reflects clinical practice because adjuvant chemotherapy was optional. The efficacy of adjuvant chemotherapy in this setting is debatable and not recommended in the national guidelines of the Netherlands, Norway, or Sweden (although all the Swedish centres except one opted for adjuvant chemotherapy in the trial). The lack of difference in disease-related treatment failure in the standard of care group, with or without a hospital policy for adjuvant chemotherapy, underlines our hypothesis that postoperative chemotherapy, in this context, is of low value.

In conclusion, despite these critical comments, we maintain that short-course radiotherapy and neoadjuvant chemotherapy is a valuable approach in the management of locally advanced rectal cancer.

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1 Bahadoer RR, Dijkstra EA, van Etten B, et al. Short-course radiotherapy followed by chemotherapy before total mesorectal excision (TME) versus preoperative chemoradiotherapy, TME, and optional adjuvant chemotherapy in locally advanced rectal cancer (RAPIDO): a randomised, open-label, phase 3 trial. *Lancet Oncol* 2021; **22:** 29–42.

2 Swedish Rectal Cancer Trial, Cedermark B, Dahlberg M, et al. Improved survival with preoperative radiotherapy in resectable rectal cancer. *N Engl J Med* 1997; **336:** 980–87.

3 Cisel B, Pietrzak L, Michalski W, et al. Long-course preoperative chemoradiation versus 5 × 5 Gy and consolidation chemotherapy for clinical T4 and fixed clinical T3 rectal cancer: long-term results of the randomized Polish II study. *Ann Oncol* 2019; **30:** 1298–303.