Authors' reply-Does the RAPIDO trial suggest a benefit of post-operative chemotherapy after preoperative chemoradiation in rectal cancer?

Zwart, W H; Dijkstra, E A; Putter, H; Marijnen, C A M; Nilsson, P J; van de Velde, C J H; van Etten, B; Hospers, G A P; Glimelius, B

Published in:
ESMO Open

DOI:
10.1016/j.esmoop.2023.101645

Publication date:
2023

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ESMO OPEN SCIENCE FOR OPTIMAL CANCER CARE

CORRESPONDENCE

Authors' reply—Does the RAPIDO trial suggest a benefit of post-operative chemotherapy after preoperative chemoradiation in rectal cancer? No, it does not

We thank Socha et al.[1] for their interest in our article regarding the value of post-operative chemotherapy (pCT) after preoperative chemoradiotherapy in the RAPIDO trial. We indeed carried out three analyses within the standard-of-care treatment and used propensity score stratification (PSS) in analyses 2 (per-protocol analysis) and 3 (compliance with pCT analysis) to correct for confounders and assure groups with balanced baseline characteristics.[2]

Although the data suggest a benefit of pCT, we agree that our analyses do not provide 'solid evidence of a gain from pCT'. Socha et al. state that the intention-to-treat (ITT) analysis (analysis 1) is 'the most appropriate method for comparing treatment efficacy'. Usually, an ITT analysis is the most robust way to compare different treatments in randomised settings. However, our ITT analysis was not carried out between randomly controlled treatments and only in one arm of a randomised trial. This was reflected by statistically significant imbalances of patient characteristics.[2] For this reason, the ITT analysis is severely biased and does not provide a fair view on the value of pCT. Therefore, PSS was used, which provides a more reliable view on the value of pCT. In addition, 22% of the patients treated at hospitals with a pCT protocol were ineligible to or did not receive pCT, which is another reason for bias in the ITT analysis. Hence, we carried out a PSS-adjusted per-protocol analysis (analysis 2), to ensure we only analysed patients who were eligible and actually treated with pCT (pCT+ group) or not (pCT− group) according to protocol.

Socha et al. suggest that analyses 2 and 3 were biased by exclusions of more patients with a poor prognosis in the pCT+ than in the pCT− group. This is incorrect, because we excluded 4/160 (pCT−) and 10/236 (pCT+) patients from analysis 2, since they were not able to start treatment with curative intention within 12 weeks after surgery (Figure 1 of the original article).[2] Of the remaining 226 patients, 42 patients excluded from the pCT+ group did not receive pCT for various reasons. At least 21/42 of these patients did not have a poor prognosis, since they had ypT2-3N0 disease or a pathological complete response. Therefore, we disagree that good prognosis patients were relatively overexpressed in the pCT− group.

Finally, Socha et al. state that PSS cannot fully compensate for every form of bias. Although this is absolutely correct, PSS is still a valuable and widely accepted statistical analysis when sufficiently powered randomised controlled trials cannot or will not be carried out.

In our opinion, our data suggest that pCT is of value after preoperative chemoradiation in patients with locally advanced rectal cancer. Our results are comparable with previously carried out randomised controlled trials that show hazard ratios for disease-free survival of ∼0.80 in favour of pCT.[3,4] Answering the question of Socha et al.: does the RAPIDO trial suggest a benefit of post-operative chemotherapy after preoperative chemoradiation in rectal cancer? Yes, it does. Does it prove it beyond doubt? No, it does not.

W. H. Zwart[1,*†], E. A. Dijkstra[1,†], H. Putter[2], C. A. M. Marijnen[3,4,‡], P. J. Nilsson[5,‡], C. J. H. van de Velde[6,‡], B. van Etten[7,‡], G. A. P. Hospers[1,‡] & B. Glimelius[8,‡]

[1]*Department of Medical Oncology, University Medical Center Groningen, University of Groningen, Groningen;*
[2]*Department of Biomedical Data Sciences, Leiden University Medical Center, Leiden;*
[3]*Department of Radiation Oncology, Netherlands Cancer Institute, Amsterdam;*
[4]*Department of Radiation Oncology, Leiden University Medical Center, Leiden, the Netherlands;*
[5]*Department of Surgery, Karolinska University Hospital, Stockholm, Sweden;*
[6]*Department of Surgery, Leiden University Medical Center, Leiden;*
[7]*Department of Surgery, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands;*
[8]*Department of Immunology, Genetics and Pathology, Uppsala University, Uppsala, Sweden*
(*E-mail: w.h.zwart@umcg.nl).

[†]Shared first authors.
[‡]Principal investigators of the RAPIDO trial.

Available online xxx

https://doi.org/10.1016/j.esmoop.2023.101645
DOI of original articles: https://doi.org/10.1016/j.esmoop.2023.101644
https://doi.org/10.1016/j.esmoop.2023.101158

FUNDING

None declared.

DISCLOSURE

The authors have declared no conflicts of interest.

REFERENCES

1. Gampenrieder SP, Dezentjé V, Lambertini M, et al. Influence of HER2 expression on prognosis in metastatic triple-negative breast cancer-results from an international, multicenter analysis coordinated by the AGMT Study Group. *ESMO Open*. 2023;8(1):100747.
2. Dijkstra EA, Zwart WH, Nilsson PJ, et al. The value of post-operative chemotherapy after chemoradiotherapy in patients with high-risk locally advanced rectal cancer-results from the RAPIDO trial. *ESMO Open*. 2023;8(2):101158.
3. Breugom AJ, Swets M, Bosset J, et al. Adjuvant chemotherapy after preoperative (chemo)radiotherapy and surgery for patients with rectal cancer: a systematic review and meta-analysis of individual patient data. *Lancet Oncol*. 2015;16(2):200-207.
4. Bujko K, Glimelius B, Valentini V, Michalski W, Spalek M. Postoperative chemotherapy in patients with rectal cancer receiving preoperative radio(chemo)therapy: a meta-analysis of randomized trials comparing surgery ± a fluoropyrimidine and surgery + a fluoropyrimidine ± oxaliplatin. *Eur J Surg Oncol*. 2015;41(6):713-723.