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Comment on "Locoregional Failure During and After Short-Course Radiotherapy Followed by Chemotherapy and Surgery Compared to Long-Course Chemoradiotherapy and Surgery: A Five-Year Follow-Up of the RAPIDO Trial"

The RAPIDO Trial Does Not Achieve Its Primary Endpoint

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We congratulate the Rectal cancer And Pre-operative Induction therapy followed by Dedicated Operation (RAPIDO) investigators for their large randomized trial that showed a significant reduction in the 5-year metastatic rate with total neoadjuvant therapy using short course 5×5 Gy radiation scheme followed by combination chemotherapy and surgery compared with a control group with long-course chemoradiotherapy followed by surgery and optional adjuvant chemotherapy in patients with high-risk locally advanced rectal cancer.[1] Final primary endpoint of this trial was disease-related treatment failure (DrTF), a new endpoint defined as the first occurrence of locoregional (LR) failure, distant metastasis, or treatment-related death, excluding deaths from other causes and second cancers except colorectal tumor.

Successive primary objectives of this trial were, first, increase in disease-free survival from 50% to 60% (2011), then a reduction in the DrTF rate at 3 years from 50% to 40% (2016); then statistical calculations and sample size were changed after an efficacy interim analysis performed after 215 DrTF events (2017). Then, the hypothesis was changed to decrease the probability of DrTF events from 30% to 22.5% with the experimental treatment (2019). Due to this interim analysis, the final analysis was planned at a nominal alpha level of 0.0424 (protocol page 48). At 5 years, the cumulative probability of DrTF was 27.8% (95% confidence interval [CI], 23.7–31.8) in the experimental group and 34.0% (95% CI, 29.6–38.4) in the standard group (hazard ratio, 0.79 [95% CI, 0.63–1.00]) with a *P*-value of 0.048, this means that statistical significance of this primary endpoint is not achieved. Five-year disease-free survival data are not presented, which precludes comparison with other randomized trials.

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As stated by the authors, this trial was aimed to reduce distant metastases without compromising LR control. Unfortunately, 5-year LR control was compromised, with a statistically significant increase in LR failures and LR recurrences (10.2% in the experimental arm *vs* 6.1% in the standard arm; *P* = 0.027). The LR rate (LRR) rate of the RAPIDO experimental arm (10.2%) is, thus, much higher than that of the 5-year PRODIGE 23 trial with induction FOLFIRINOX followed by radiochemotherapy (4.7%), whereas the LRR rates of the standard arms of the 2 trials are of the same order around 6% (unpublished data update).[2]

This result is not surprising considering the intensity of the LR treatment delivered in each of the 2 arms. In the standard arm, the treatment was standard-dose radiochemotherapy followed by surgery performed within the usual time frame. On the contrary, the experimental arm used a short-course radiotherapy but a delay of 40 weeks until surgery. The 5×5 Gy short-course radiotherapy delivered a biological dose equivalent to 2 Gy per fraction from 31.3 Gy (for alpha/beta = 10) to 35.7 Gy (for alpha/beta = 5) according to the linear quadratic model, which was significantly lower than the standard arm.[3,4] If this lower biological dose equivalent is not a problem in the immediate preoperative setting when complete surgery can be performed, it probably explains the worse LR control results in this trial where the surgery was staggered. Glynne-Jones et al[5] have suggested as additional explanations for greater LRR a possible treatment-induced tumor fragmentation and the operative difficulties induced by delayed surgery.

Finally, quality assurance in multicenter trials involving radiotherapy is essential to ensure consistency of practice. In the RAPIDO trial, no dummy-run or centralized review of radiotherapy volumes was performed. In this respect, the large number of presacred recurrences in the experimental arm raises questions about the volume of treatment performed in these cases.[6,7]

In conclusion, the RAPIDO trial did not achieve its primary objective because of a higher LRR in the experimental arm, which might be explained by a nonoptimal radiotherapy.

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