READ IT BEFORE YOUR PATIENTS

Rectal

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

Renu R Bahadoer, Esmée A Dijkstra, Boudewijn van Etten, Corrie A M Marijnen, Hein Putter, Elma Meershoek-Klein Kranenbarg, Annet G H Roodvoets, Iris D Nagtegaal, Regina G H Beets-Tan, Lennart K Blomqvist, Tone Fokstuen, Albert J Ten Tije, Jaume Capdevila, Mathijs P Hendriks, Ibrahim Edhemovic, Andrés Cervantes, Per J Nilsson, Bengt Glimelius, Cornelis J H van de Velde, Geke A P Hospers 1, RAPIDO collaborative investigators

Lancet Oncol. 2020 Dec 7;S1470-2045(20)30555-6. doi: 10.1016/S1470-2045(20)30555-6. Online ahead of print.

BACKGROUND

Systemic relapses remain a major problem in locally advanced rectal cancer. Using short-course radiotherapy followed by chemotherapy and delayed surgery, the Rectal cancer And Preoperative Induction therapy followed by Dedicated Operation (RAPIDO) trial aimed to reduce distant metastases without compromising locoregional control.

METHODS

In this multicentre, open-label, randomised, controlled, phase 3 trial, participants were recruited from 54 centres in the Netherlands, Sweden, Spain, Slovenia, Denmark, Norway, and the USA. Patients were eligible if they were aged 18 years or older, with an Eastern Cooperative Oncology Group (ECOG) performance status of 0-1, had a biopsy-proven, newly diagnosed, primary, locally advanced rectal adenocarcinoma, which was classified as high risk on pelvic MRI (with at least one of the following criteria: clinical tumour [cT] stage cT4a or cT4b, extramural vascular invasion, clinical nodal [cN] stage cN2, involved mesorectal fascia, or enlarged lateral lymph nodes), were mentally and physically fit for chemotherapy, and could be assessed for staging within 5 weeks before randomisation. Eligible participants were randomly assigned (1:1), using a management system with a randomly varying block design (each block size randomly chosen to contain two to four allocations), stratified by centre, ECOG performance status, cT stage, and cN stage, to either the experimental or standard of care group. All investigators remained masked for the primary endpoint until a prespecified number of events was reached. Patients allocated to the experimental treatment group received short-course radiotherapy (5 × 5 Gy over a maximum of 8 days) followed by six cycles of CAPOX chemotherapy (capecitabine 1000 mg/m2 orally twice daily on days 1-14, oxaliplatin 130 mg/m2 intravenously on day 1, and a chemotherapy-free interval between days 15-21) or nine cycles of FOLFOX4 (oxaliplatin 85 mg/m2 intravenously on day 1, leucovorin [folinic acid] 200 mg/m2 intravenously on days 1 and 2, followed by bolus fluorouracil 400 mg/m2 intravenously and fluorouracil 600 mg/m2 intravenously for 22 h on days 1 and 2, and a chemotherapy-free interval between days 3-14) followed by total mesorectal excision. Choice of CAPOX or FOLFOX4 was per physician discretion or hospital policy. Patients allocated to the standard of care group received 28 daily fractions of 1·8 Gy up to 50·4 Gy or 25 fractions of 2·0 Gy up to 50·0 Gy (per physician discretion or hospital policy), with concomitant twice-daily oral capecitabine 825 mg/m2 followed by total mesorectal excision and, if stipulated by hospital policy, adjuvant chemotherapy with eight cycles of CAPOX or 12 cycles of FOLFOX4. The primary endpoint was 3-year disease-related treatment failure, defined as the first occurrence of locoregional failure, distant metastasis, new primary colorectal tumour, or treatment-related death, assessed in the intention-to-treat population. Safety was assessed by intention to treat. This study is registered with the EudraCT, 2010-023957-12, and ClinicalTrials.gov, NCT01558921, and is now complete.

FINDINGS

Between June 21, 2011, and June 2, 2016, 920 patients were enrolled and randomly assigned to a treatment, of whom 912 were eligible (462 in the experimental group; 450 in the standard of care group). Median follow-up was 4·6 years (IQR 3·5-5·5). At 3 years after randomisation, the cumulative probability of disease-related treatment failure was 23·7% (95% CI 19·8-27·6) in the experimental group versus 30·4% (26·1-34·6) in the standard of care group (hazard ratio 0·75, 95% CI 0·60-0·95; p=0·019). The most common grade 3 or higher adverse event during preoperative therapy in both groups was diarrhoea (81 [18%] of 460 patients in the experimental group and 41 [9%] of 441 in the standard of care group) and neurological toxicity during adjuvant chemotherapy in the standard of care group (16 [9%] of 187 patients). Serious adverse events occurred in 177 (38%) of 460 participants in the experimental group and, in the standard of care group, in 87 (34%) of 254 patients without adjuvant chemotherapy and in 64 (34%) of 187 with adjuvant chemotherapy. Treatment-related deaths occurred in four participants in the experimental group (one cardiac arrest, one pulmonary embolism, two infectious complications) and in four participants in the standard of care group (one pulmonary embolism, one neutropenic sepsis, one aspiration, one suicide due to severe depression).

INTERPRETATION

The observed decreased probability of disease-related treatment failure in the experimental group is probably indicative of the increased efficacy of preoperative chemotherapy as opposed to adjuvant chemotherapy in this setting. Therefore, the experimental treatment can be considered as a new standard of care in high-risk locally advanced rectal cancer.