# Neoadjuvant chemoradiotherapy with radiation dose escalation with contact x-ray brachytherapy boost or external beam radiotherapy boost for organ preservation in early cT2-cT3 rectal adenocarcinoma (OPERA): a phase 3, randomised controlled trial

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## *Abstract*

### BACKGROUND

Organ preservation after reaching clinical complete response on neoadjuvant therapy is gaining interest for rectal cancers, although the role of radiation dose escalation is still not known. We aimed to determine whether a contact x-ray brachytherapy boost, following or preceding neoadjuvant chemoradiotherapy, increases the probability of 3-year organ preservation for patients with early rectal cancers.

### METHODS

OPERA was a multicentre, open-label, phase 3 randomised controlled trial done at 17 cancer centres that included operable patients, aged 18 years or older, with cT2, cT3a, or cT3b adenocarcinoma of low-mid rectum, tumours of less than 5 cm in diameter, and cN0 or cN1 smaller than 8 mm. All patients received neoadjuvant chemoradiotherapy and 45 Gy external beam radiotherapy in 25 fractions over 5 weeks with concurrent oral capecitabine (825 mg/m2 twice a day). Patients were randomly assigned (1:1) to receive a boost of external beam radiotherapy at 9 Gy in five fractions (group A) or a boost with contact x-ray brachytherapy (90 Gy in three fractions; group B). Randomisation was done centrally using an independent web-based system and stratified by trial centre, tumour classification (cT2 vs cT3a or cT3b), tumour distance from rectum (<6 cm from anal verge vs ≥6 cm), and tumour diameter (<3 cm vs ≥3 cm). Treatment in group B was stratified by tumour diameter, with the contact x-ray brachytherapy boost given before neoadjuvant chemoradiotherapy in patients with tumours smaller than 3 cm. The primary outcome was organ preservation at 3 years, analysed in the modified intention-to-treat population. This study was registered with ClinicalTrials.gov, NCT02505750, and is ongoing.

### FINDINGS

Between June 14, 2015, and June 26, 2020, 148 patients were assessed for eligibility and were randomly assigned to group A (n=74) or group B (n=74). Seven patients withdrew their consent (five in group A and two in group B). 141 patients were included in the primary efficacy analysis, including 69 assigned to group A (29 with tumours <3 cm in diameter and 40 with tumours ≥3 cm) and 72 assigned to group B (32 with tumours <3 cm and 40 with tumours ≥3 cm). After a median follow-up of 38·2 months (IQR 34·2-42·5), the 3-year organ preservation rate was 59% (95% CI 48-72) in group A versus 81% (72-91) in group B (hazard ratio [HR] 0·36, 95% CI 0·19-0·70; p=0·0026). For patients with tumours less than 3 cm in diameter, 3-year organ preservation rates were 63% (95% CI 47-84) in group A versus 97% (91-100) in group B (HR 0·07, 95% CI 0·01-0·57; p=0·012). For patients with tumours of 3 cm or larger, 3-year organ preservation rates were 55% (95% CI 41-74) in group A versus 68% (54-85) in group B (HR 0·54, 95% CI 0·26-1·10; p=0·11). 21 (30%) patients in group A and 30 (42%) in group B had an early grade 2-3 adverse event (p=1·0). The most common early grade 2-3 adverse events were proctitis (four [6%] in group A, nine [13%] in group B) and radiation dermatitis (seven [10%] in

group A, two [3%] in group B). The main late side-effect was grade 1-2 rectal bleeding due to telangiectasia, which was more frequent in group B (37 [63%] of 59) than in group A (five [12%] of 43; p<0·0001) and subsided after 3 years.

## INTERPRETATION

Neoadjuvant chemoradiotherapy with a contact x-ray brachytherapy boost significantly improved the 3-year organ preservation rate, particularly for patients with tumours smaller than 3 cm who were treated with contact x-ray brachytherapy first, compared with neoadjuvant chemoradiotherapy with a boost via external beam radiotherapy. This approach could be discussed and offered to operable patients with early cT2-cT3 disease who are keen to avoid surgery and seek organ preservation.