Dysphagia-optimised intensity-modulated radiotherapy versus standard intensity-modulated radiotherapy in patients with head and neck cancer (DARS): a phase 3, multicentre, randomised, controlled trial

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Background:
Most newly diagnosed oropharyngeal and hypopharyngeal cancers are treated with chemoradiotherapy with curative intent but at the consequence of adverse effects on quality of life. We aimed to investigate if dysphagia-optimised intensity-modulated radiotherapy (DO-IMRT) reduced radiation dose to the dysphagia and aspiration related structures and improved swallowing function compared with standard IMRT.

Methods:
DARS was a parallel-group, phase 3, multicentre, randomised, controlled trial done in 22 radiotherapy centres in Ireland and the UK. Participants were aged 18 years and older, had T1-4, N0-3, M0 oropharyngeal or hypopharyngeal cancer, a WHO performance status of 0 or 1, and no pre-existing swallowing dysfunction. Participants were centrally randomly assigned (1:1) using a minimisation algorithm (balancing factors: centre, chemotherapy use, tumour type, American Joint Committee on Cancer tumour stage) to receive DO-IMRT or standard IMRT. Participants and speech language therapists were masked to treatment allocation. Radiotherapy was given in 30 fractions over 6 weeks. Dose was 65 Gy to primary and nodal tumour and 54 Gy to remaining pharyngeal subsite and nodal areas at risk of microscopic disease. For DO-IMRT, the volume of the superior and middle pharyngeal constrictor muscle or inferior pharyngeal constrictor muscle lying outside the high-dose target volume had a mandatory 50 Gy mean dose constraint. The primary endpoint was MD Anderson Dysphagia Inventory (MDADI) composite score 12 months after radiotherapy, analysed in the modified intention-to-treat population that included only patients who completed a 12-month assessment; safety was assessed in all randomly assigned patients who received at least one fraction of radiotherapy. The study is registered with the ISRCTN registry, ISRCTN25458988, and is complete.

Findings:
From June 24, 2016, to April 27, 2018, 118 patients were registered, 112 of whom were randomly assigned (56 to each treatment group). 22 (20%) participants were female and 90 (80%) were male; median age was 57 years (IQR 52-62). Median follow-up was 39·5 months (IQR 37·8-50·0). Patients in the DO-IMRT group had significantly higher MDADI composite scores at 12 months than patients in the standard IMRT group (mean score 77·7 [SD 16·1] vs 70·6 [17·3]; mean difference 7·2 [95% CI 0·4-13·9]; p=0·037). 25 serious adverse events (16 serious adverse events assessed as unrelated to study treatment [nine in the DO-IMRT group and seven in the standard IMRT group] and nine serious adverse reactions [two vs seven]) were reported in 23 patients. The most common grade 3-4 late adverse events were hearing impairment (nine [16%] of 55 in the DO-IMRT group vs seven [13%] of 55 in the standard IMRT group), dry mouth (three [5%] vs eight [15%]), and dysphagia (three [5%] vs eight [15%]). There were no treatment-related deaths.

Interpretation:
Our findings suggest that DO-IMRT improves patient-reported swallowing function compared with standard IMRT. DO-IMRT should be considered a new standard of care for patients receiving radiotherapy for pharyngeal cancers.