Bladder

Hypofractionated radiotherapy in locally advanced bladder cancer: an individual patient data meta-analysis of the BC2001 and BCON trials

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BACKGROUND

Two radiotherapy fractionation schedules are used to treat locally advanced bladder cancer: 64 Gy in 32 fractions over 6·5 weeks and a hypofractionated schedule of 55 Gy in 20 fractions over four weeks. Long-term outcomes of these schedules in several cohort studies and case series suggest that response, survival, and toxicity are similar, but no direct comparison has been published. The present study aimed to assess the non-inferiority of 55 Gy in 20 fractions to 64 Gy in 32 fractions in terms of invasive locoregional control and late toxicity in patients with locally advanced bladder cancer.

METHODS

We did a meta-analysis of individual patient data from patients (age ≥18 years) with locally advanced bladder cancer (T1G3 [high-grade non-muscle invasive] or T2–T4, N0M0) enrolled in two multicentre, randomised, controlled, phase III trials done in the UK: BC2001 (NCT00024349; assessing addition of chemotherapy to radiotherapy) and BCON (NCT00033436; assessing hypoxia-modifying therapy combined with radiotherapy). In each trial, the fractionation schedule was chosen according to local standard practice. Co-primary endpoints were invasive locoregional control (non-inferiority margin hazard ratio [HR]=1·25); and late bladder or rectum toxicity, assessed with the Late Effects Normal Tissue Task Force-Subjective, Objective, Management, Analytic tool (non-inferiority margin for absolute risk difference [RD]=10%). If non-inferiority was met for invasive locoregional control, superiority could be considered if the 95% CI for the treatment effect excluded the null effect (HR=1). One-stage individual patient data meta-analysis models for the time-to-event and binary outcomes were used, accounting for trial differences, within-centre correlation, randomised treatment received, baseline variable imbalances, and potential confounding from relevant prognostic factors.

FINDINGS

782 patients with known fractionation schedules (456 from the BC2001 trial and 326 from the BCON trial; 376 (48%) received 64 Gy in 32 fractions and 406 (52%) received 55 Gy in 20 fractions) were included in our meta-analysis. Median follow-up was 120 months (IQR 99–159). Patients who received 55 Gy in 20 fractions had a lower risk of invasive locoregional recurrence than those who received 64 Gy in 32 fractions (adjusted HR 0·71 [95% CI 0·52–0·96]). Both schedules had similar toxicity profiles (adjusted RD −3·37% [95% CI −11·85 to 5·10]).

INTERPRETATION

A hypofractionated schedule of 55 Gy in 20 fractions is non-inferior to 64 Gy in 32 fractions with regard to both invasive locoregional control and toxicity, and is superior with regard to invasive locoregional control. 55 Gy in 20 fractions should be adopted as a standard of care for bladder preservation in patients with locally advanced bladder cancer.