Prostate

Adjuvant radiotherapy versus early salvage radiotherapy following radical prostatectomy (TROG 08.03/ANZUP RAVES): a randomised, controlled, phase III, non-inferiority trial.

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BACKGROUND

Adjuvant radiotherapy has been shown to halve the risk of biochemical progression for patients with high-risk disease after radical prostatectomy. Early salvage radiotherapy could result in similar biochemical control with lower treatment toxicity. We aimed to compare biochemical progression between patients given adjuvant radiotherapy and those given salvage radiotherapy.

METHODS

We did a phase III, randomised, controlled, non-inferiority trial across 32 oncology centres in Australia and New Zealand. Eligible patients were aged at least 18 years and had undergone a radical prostatectomy for adenocarcinoma of the prostate with pathological staging showing high-risk features defined as positive surgical margins, extraprostatic extension, or seminal vesicle invasion; had an Eastern Cooperative Oncology Group performance status of 0-1, and had a postoperative prostate-specific antigen (PSA) concentration of 0·10 ng/mL or less. Patients were randomly assigned (1:1) using a minimisation technique via an internet-based, independently generated allocation to either adjuvant radiotherapy within six months of radical prostatectomy or early salvage radiotherapy triggered by a PSA of 0·20 ng/mL or more. Allocation sequence was concealed from investigators and patients, but treatment assignment for individual randomisations was not masked. Patients were stratified by radiotherapy centre, preoperative PSA, Gleason score, surgical margin status, and seminal vesicle invasion status. Radiotherapy in both groups was 64 Gy in 32 fractions to the prostate bed without androgen deprivation therapy with real-time review of plan quality on all cases before treatment. The primary endpoint was freedom from biochemical progression. Salvage radiotherapy would be deemed non-inferior to adjuvant radiotherapy if freedom from biochemical progression at five years was within 10% of that for adjuvant radiotherapy with a hazard ratio (HR) for salvage radiotherapy versus adjuvant radiotherapy of 1·48. The primary analysis was done on an intention-to-treat basis. This study is registered with ClinicalTrials.gov, NCT00860652.

FINDINGS

Between 27 March 2009, and 31 December, 2015, 333 patients were randomly assigned (166 to adjuvant radiotherapy; 167 to salvage radiotherapy). Median follow-up was 6·1 years (IQR 4·3-7·5). An independent data monitoring committee recommended premature closure of enrolment because of unexpectedly low event rates. 84 (50%) patients in the salvage radiotherapy group had radiotherapy triggered by a PSA of 0·20 ng/mL or more. Five-year freedom from biochemical progression was 86% (95% CI 81-92) in the adjuvant radiotherapy group versus 87% (82-93) in the salvage radiotherapy group (stratified HR 1·12, 95% CI 0·65-1·90; pnon-inferiority=0·15). The grade 2 or worse genitourinary toxicity rate was lower in the salvage radiotherapy group (90 [54%] of 167) than in the adjuvant radiotherapy group (116 [70%] of 166). The grade 2 or worse gastrointestinal toxicity rate was similar between the salvage radiotherapy group (16 [10%]) and the adjuvant radiotherapy group (24 [14%]).

INTERPRETATION

Salvage radiotherapy did not meet trial specified criteria for non-inferiority. However, these data support the use of salvage radiotherapy as it results in similar biochemical control to adjuvant radiotherapy, spares around half of men from pelvic radiation, and is associated with significantly lower genitourinary toxicity.