Prostate

Timing of radiotherapy after radical prostatectomy (RADICALS-RT): a randomised, controlled phase 3 trial.

Parker CC, Clarke NW, Cook AD, Kynaston HG, Petersen PM, Catton C, Cross W, Logue J, Parulekar W, Payne H, Persad R, Pickering H, Saad F, Anderson J, Bahl A, Bottomley D, Brasso K, Chahal R, Cooke PW, Eddy B, Gibbs S, Goh C, Gujral S, Heath C, Henderson A, Jaganathan R, Jakobsen H, James ND, Kanaga Sundaram S, Lees K, Lester J, Lindberg H, Money-Kyrle J, Morris S, O'Sullivan J, Ostler P, Owen L, Patel P, Pope A, Popert R, Raman R, Røder MA, Sayers I, Simms M, Wilson J, Zarkar A, Parmar MKB, Sydes MR.

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BACKGROUND

The optimal timing of radiotherapy after radical prostatectomy for prostate cancer is uncertain. We aimed to compare the efficacy and safety of adjuvant radiotherapy versus an observation policy with salvage radiotherapy for prostate-specific antigen (PSA) biochemical progression.

METHODS

We did a randomised controlled trial enrolling patients with at least one risk factor (pathological T-stage three or four, Gleason score of 7-10, positive margins, or preoperative PSA ≥10 ng/mL) for biochemical progression after radical prostatectomy (RADICALS-RT). The study took place in trial-accredited centres in Canada, Denmark, Ireland, and the UK. Patients were randomly assigned in a 1:1 ratio to adjuvant radiotherapy or an observation policy with salvage radiotherapy for PSA biochemical progression (PSA ≥0·1 ng/mL or three consecutive rises). Masking was not deemed feasible. Stratification factors were Gleason score, margin status, planned radiotherapy schedule (52·5 Gy in 20 fractions or 66 Gy in 33 fractions), and centre. The primary outcome measure was freedom from distant metastases, designed with 80% power to detect an improvement from 90% with salvage radiotherapy (control) to 95% at 10 years with adjuvant radiotherapy. We report on biochemical progression-free survival, freedom from non-protocol hormone therapy, safety, and patient-reported outcomes. Standard survival analysis methods were used. A hazard ratio (HR) of less than one favoured adjuvant radiotherapy. This study is registered with ClinicalTrials.gov, NCT00541047.

FINDINGS

Between 22 November 2007, and 30 December 2016, 1396 patients were randomly assigned, 699 (50%) to salvage radiotherapy and 697 (50%) to adjuvant radiotherapy. Allocated groups were balanced with a median age of 65 years (IQR 60-68). Median follow-up was 4·9 years (IQR 3·0-6·1). 649 (93%) of 697 participants in the adjuvant radiotherapy group reported radiotherapy within six months; 228 (33%) of 699 in the salvage radiotherapy group reported radiotherapy within eight years after randomisation. With 169 events, five-year biochemical progression-free survival was 85% for those in the adjuvant radiotherapy group and 88% for those in the salvage radiotherapy group (HR 1·10, 95% CI 0·81-1·49; p=0·56). Freedom from non-protocol hormone therapy at five years was 93% for those in the adjuvant radiotherapy group versus 92% for those in the salvage radiotherapy group (HR 0·88, 95% CI 0·58-1·33; p=0·53). Self-reported urinary incontinence was worse at one year for those in the adjuvant radiotherapy group (mean score 4·8 vs 4·0; p=0·0023). Grade 3.0-4.0 urethral stricture within two years was reported in 6% of individuals in the adjuvant radiotherapy group versus 4.0% in the salvage radiotherapy group (p=0·020).

INTERPRETATION

These initial results do not support routine administration of adjuvant radiotherapy after radical prostatectomy. Adjuvant radiotherapy increases the risk of urinary morbidity. An observation policy with salvage radiotherapy for PSA biochemical progression should be the current standard after radical prostatectomy.