The use of conformal radiotherapy and the selection of radiation dose in T1 or T2 prostate cancer


CRD summary
This review evaluated the effects of conformal radiotherapy (CR) versus conventional external-beam radiotherapy for treating clinically localised prostate cancer. The authors concluded that CR should be preferred to conventional radiotherapy. The review had some methodological limitations and the evidence base reviewed was small, but the conclusions seem appropriate. However, further randomised controlled trials are needed to confirm these findings.

Authors' objectives
To evaluate the role of three-dimensional (3-D) conformal radiotherapy (CR) in treating clinically localised prostate cancer, and to determine the appropriate dose and fractionation prescription for this clinical setting.

Searching
MEDLINE (from 1991 to March 2002) and Cancerlit (from 1991 to October 2001) were searched; the search terms were reported. The authors also searched the proceedings of the 1999, 2000 and 2001 meetings of the American Society of Clinical Oncology and the American Society for Therapeutic Radiology and Oncology for reports of recently completed trials, and the PDQ clinical trials database for ongoing trials. Additional items were retrieved from personal files and by scanning reference lists. Publications in languages other than English were excluded.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) comparing CR with conventional external-beam radiotherapy were eligible for inclusion. Non-randomised comparative studies were also eligible, provided that patients were treated according to a prospective clinical trial protocol (phase II studies) or comparisons were made using sequential prospective patient cohorts and/or appropriate multivariate analyses of institutional data.

Specific interventions included in the review
The intervention of interest was 3-D CR. Studies comparing CR with conventional external-beam radiotherapy were eligible for inclusion, as were comparative studies evaluating radiotherapy dose escalation and conformal treatment delivery. The CR doses in the included studies ranged from 64 to 81 Gy.

Participants included in the review
Eligible participants were men with clinically localised prostate cancer (T1 or T2 with clinical nodal staging (N0-NX) and a Gleason score of 7 or less). There was no pre-specified upper limit of prostate-specific antigen (PSA).

Outcomes assessed in the review
The studies were required to report one or more of the following outcomes: overall survival; surrogate end points such as serum PSA control rates and post-treatment prostate biopsy results; biochemical freedom from failure (bNED); or other disease outcome measures such as clinical recurrence-free survival and disease-specific survival. Comparative studies were eligible for inclusion if they reported toxicity outcomes or technical outcomes (improved dose distribution, reproducibility or target delineation). The included studies reported overall survival, bNED (most commonly expressed as 5-year actuarial survival) and/or toxicity (mainly gastrointestinal and/or genitourinary).

How were decisions on the relevance of primary studies made?
One reviewer selected papers for the review.
Assessment of study quality
The authors did not state what criteria were used to assess the validity of the RCTs. Non-randomised comparative studies were rated as well-conducted if all patients were accounted for in the reports, the treatments were appropriately described, they were conducted in large centres and the statistical analysis was appropriate. The authors did not state how the papers were assessed for validity, or how many reviewers performed the validity assessment.

Data extraction
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction assessment. Five-year actuarial survival and other disease-related outcomes were extracted for each treatment group. The percentages of patients with acute and or late toxicity were extracted by treatment group, site and grade of toxicity.

Methods of synthesis
How were the studies combined?
The studies were grouped firstly by outcome and secondly by study design, and combined in a narrative. The authors did not state that they assessed publication bias, although they did state that they were not aware of any relevant unpublished data.

How were differences between studies investigated?
The authors did not state that they formally assessed statistical heterogeneity. However, the results from RCTs were not pooled because of differences in study design and outcomes.

Results of the review
For disease-related outcomes, 2 RCTs (526 participants) and 9 phase II or non-randomised comparative studies (7,254 participants) were included. For toxicity outcomes, 3 RCTs (over 323 patients; the number of participants in one trial varied between outcomes) provided data on acute toxicity and 3 further RCTs (483 evaluable participants) provided data on late toxicity. Ten phase II or non-randomised comparative studies (3,698 participants) were also included in the evaluation of toxicity outcomes.

Disease-related outcomes.
In one RCT of CR versus conventional radiotherapy, the difference in bNED between groups did not reach statistical significance. There was a statistically significant improvement in bNED in favour of CR in patients with T1 or T2 disease and pre-treatment PSA greater than 10. In a second RCT, bNED rates for CR versus conventional radiotherapy were 71% versus 54% (figures given as 5-year rates in the tables and 2-year rates in the text). Non-comparative studies gave contradictory results on the relationship between radiotherapy dose and bNED.

Toxicity-related outcomes.
Three RCTs of CR versus conventional radiotherapy provided data on acute toxicity. In two of these, CR reduced toxicity compared with conventional radiotherapy at the same dose. In the third RCT, a higher dose was used in the CR arm but acute toxicity did not differ significantly between groups. Three different RCTs of CR versus conventional radiotherapy provided data on late toxicity (occurring 1 year or more after treatment). Two trials in which a higher dose was used in the CR arm reported no significant differences in late bladder or bowel toxicity. In the third RCT, patients received the same dose in both arms and grade 2 or greater bowel toxicity was significantly more common in the conventional radiotherapy arm. Toxicity data from non-comparative studies were also reported.

Authors’ conclusions
Evidence from RCTs indicated that the use of CR without dose escalation reduces the rates of both early and late bowel and bladder toxicity. Evidence from prospective cohort studies and one RCT appeared to indicate that dose escalation with CR (above that delivered by conventional radiotherapy) increases bNED rates without increasing toxicity. In non-
randomised studies, the most consistent benefit of dose escalation on bNED is seen in patients with intermediate-risk disease (PSA 10 to 20 ng/mL).

CRD commentary
This review addressed two distinct questions with inclusion criteria for study design that were different, but clearly defined, for the two questions. The authors searched a range of relevant sources, although the search was confined to English language items, which could have introduced language or publication bias into the review. The authors did not assess the validity of the included studies, so it is possible that these studies and the synthesis derived from them may not be reliable. It appeared that a single reviewer selected papers for the review; independent selection by two reviewers would have reduced the risk of introducing bias and errors during the selection process. Relevant details of the included studies were tabulated. The authors did not formally evaluate heterogeneity, but they recognised the importance of the issue and their decision not to pool the data would appear appropriate. The authors’ conclusions reflect the evidence presented and, despite the methodological limitations of the review, are likely to be reasonably reliable.

Implications of the review for practice and research
Practice: The authors stated that patients receiving external-beam radiotherapy should be treated using a 3-D conformal technique. For dose escalation, patients should be offered participation in RCTs if possible. In the absence of such trials, patients with intermediate-risk disease treated with external-beam radiotherapy alone should be offered doses of 75 to 78 Gy in 180 to 200 cGy fractions.

Research: The authors stated that there is a need for further studies to confirm the benefits of dose escalation when CR is used.

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Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.