Intensity-modulated radiotherapy for the treatment of prostate cancer: a systematic review and economic evaluation

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CRD summary
This review concluded that comparative data of intensity modulated radiotherapy with three-dimensional conformal radiotherapy appeared to support the theory that higher doses can improve biochemical survival with localised prostate cancer. These conclusions should be interpreted with caution due to the possibility of language bias, limited quality of the included studies and a lack of rigour in the review process.

Authors' objectives
To assess the effectiveness of intensity-modulated radiotherapy for the radical treatment of prostate cancer.

This abstract addresses only the clinical effectiveness part of the report.

Searching
Fifteen electronic bibliographic databases (included MEDLINE, EMBASE, CINAHL, BIOSIS, Cochrane Database of Systematic Reviews, Cochrane Central Register of Systematic Reviews, DARE and Science Citation Index) were searched up to January 2009. An updated search was performed in May 2009. Search terms were reported. Relevant research registers and conference proceedings were searched. Reference lists of retrieved studies and relevant systematic reviews were handsearched. Studies published in languages other than English were excluded.

Study selection
Studies of intensity modulated radiotherapy (with systems that did or did not combine the ability to simultaneously image, whether delivered using forward planning or inverse planning) compared with three-dimensional conformal radiotherapy or radical prostatectomy in men with prostate cancer for whom radical radiotherapy was appropriate were eligible for inclusion. The review outcomes were overall and disease-specific survival, progression-free survival (clinical or biochemical relapse free), adverse effects and health-related quality of life (HRQoL).

All of the included studies compared intensity-modulated radiotherapy with three dimensional conformal radiotherapy. No studies were identified that compared intensity-modulated radiotherapy with radical prostatectomy. Where reported, most of the included studies were of localised prostate cancer; the other studies were of locally advanced prostate cancer. The mean/median age of included patients ranged from 62 to 72.6 years. Nearly half of the included studies used historical controls. Treatments varied between the included studies in terms of planning target volume, dose, dose constraints, fractionation and patient positioning. Where reported, radiation dose in five studies was higher in the intensity-modulated radiotherapy group and radiation dose in three studies was similar between treatment groups. Patients in most studies were evaluated at three- to six-month treatment intervals. The included studies were conducted in USA, Italy, Japan and The Netherlands. None of the included studies were set in UK, but the authors stated that patients and treatments in these studies were of relevance to UK practice.

One reviewer assessed studies for inclusion, with involvement of a second reviewer when necessary.

Assessment of study quality
The quality of studies was assessed using the adapted Downs and Black checklist for appropriateness and adequate description of hypotheses, study design, intervention and main outcomes, methods of analyses, methods of data collection, loss to follow-up and treatment group comparison. It was not possible to perform a full quality assessment for studies presented in abstract form, due to the limited information available.

One reviewer performed validity assessment.

Data extraction
One reviewer extracted data on event rates using a standardised form.
Methods of synthesis
The studies were combined in a narrative analysis supported by data tables.

Results of the review
Thirteen non-randomised studies were included in the review: eight full papers (2,767 participants, ranged 27 to 1,571) and five abstracts. Four studies were retrospective patient records studies. Three studies were prospective comparisons of case series. One study retrospectively selected patients from one of those prospective studies.

All eight fully published studies had a medium to high risk of bias. All eight studies reported an aim or hypothesis and clearly described the intervention. Seven studies clearly described main outcomes. Only one study had similar population characteristics between treatment groups. Seven studies had the same data collection methods per group. Four studies clearly or partially described confounders. Only five studies adjusted for different lengths of follow-up in analyses. None of the studies reported loss to follow-up.

None of the studies reported overall survival or clinically-measured disease-free survival. One abstract reported no significant difference between treatment groups in distant metastasis or cause-specific mortality at four-year follow-up.

Two studies reported no significant difference in biochemical relapse-free survival between treatment groups. One study found a significant biochemical survival advantage for intensity modulated radiotherapy. This difference was probably explained by dose: there was a dose difference between treatment groups in which higher dose intensity modulated radiotherapy was favoured over lower dose three-dimensional conformal radiotherapy.

Among all studies, there was no clear reporting of treatment-related deaths. None of the studies reported secondary malignancies. Most studies reported that intensity modulated radiotherapy was associated with an advantage in gastrointestinal toxicity, attributed to increased conformality of treatment, in particular the volume of rectum treated.

Authors' conclusions
The comparative data of intensity modulated radiotherapy with three-dimensional conformal radiotherapy appeared to support the theory that higher doses can improve biochemical survival for patients with localised prostate cancer, concurring with data on conformal radiotherapy. Intensity modulated radiotherapy reduced toxicity, particularly with regard to gastrointestinal toxicity.

CRD commentary
This review's inclusion criteria were clear. Fifteen relevant databases were searched. Efforts were made to find both published and unpublished studies, which minimised potential for publication bias. The decision to restrict the review to studies in English increased the risk of language bias. Insufficient attempts were made to minimise reviewer biases and errors in the review process (only one reviewer performed the study selection, quality assessment and data extraction). Appropriate criteria were used to examine study quality.

A narrative synthesis was appropriate given the diversity between the included studies. The authors acknowledged that the strength of evidence was limited by a lack of data from randomised controlled trials.

The authors' conclusions should be interpreted with caution, given the possibility of language bias, limited quality of included studies and lack of rigour at all the stages of the review process.

Implications of the review for practice and research
Practice: The authors stated that three-dimensional conformal radiotherapy may be safely delivered at the recommended total dose of 74 Gy.

Research: The authors stated that further randomised controlled trials were required to investigate the clinical effectiveness of intensity modulated radiotherapy compared with three-dimensional conformal radiotherapy. Further studies were required for radiation to the prostate alone and for whole pelvis radiation. Dose escalation studies for intensity modulated radiotherapy were required to investigate how prostate-specific antigen survival and adverse effects varied with dose. Future studies should consider stratification by different risk groups, have adequate follow-up (at least five years) to capture late adverse events and should include HRQoL (ideally involving the EQ-5D measure). Such studies should report the evolution of adverse events with time. Studies with a long follow-up of at least 10 years and a
large sample size were required to detect group differences in secondary malignancies. Whether secondary malignancies were an issue should be addressed through registry studies.

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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.