Higher-than-conventional radiation doses in localized prostate cancer treatment: a meta-analysis of randomized, controlled trials

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CRD summary
The authors concluded that high-dose radiotherapy was superior to conventional-dose radiotherapy in preventing biochemical failure in low, intermediate and high-risk men with localized prostate cancer. Evidence appeared to support the authors’ conclusions, but incomplete reporting of review methods and lack of a trial quality assessment makes it difficult to assess their reliability.

Authors' objectives
To compare high-dose radiotherapy with conventional-dose radiotherapy in the treatment of men with localized prostate cancer.

Searching
MEDLINE, EMBASE, CANCERLIT and the Cochrane Library were searched from 1996 to December 2007. Search terms were reported. The Physicians Data Query clinical trial database, proceedings of annual meetings of the American Society of Clinical Oncology (1997 to 2007) and reference lists were also searched. Studies had to either be complete reports published in peer-reviewed journals or full details had to be available from the researchers.

Study selection
Randomised controlled trials (RCTs) that compared high-dose radiotherapy with conventional-dose radiotherapy in men with histologically confirmed localized prostate cancer were eligible for inclusion. Trials of men who had metastatic disease or who had undergone previous pelvic radiotherapy, radical prostatectomy or androgen deprivation therapy were excluded. High-dose and conventional-dose radiotherapy could consist of photon or proton therapy or combinations of external beam radiotherapy and brachytherapy. Trials that compared patients with versus without androgen deprivation were eligible.

The review assessed biochemical failure (defined according to the American Society for Therapeutic Radiology and Oncology criteria), mortality, prostate cancer-specific mortality and grade two or more morbidity (according to Radiation Therapy Oncology Group Morbidity scales) due to gastrointestinal and genitourinary late toxicity.

The included studies were in low, intermediate and high-risk patients.

Two reviewers independently selected studies. Disagreements were resolved by a third reviewer.

Assessment of study quality
The authors did not state that they assessed validity.

Data extraction
Intention-to-treat data were extracted to allow calculation of odds ratios (OR) and 99% confidence intervals (CI).

The authors did not state how many reviewers performed the data extraction.

Methods of synthesis
Pooled weighted risk ratios (RR) with 99% confidence intervals were calculated for categorical data using the Peto method. Heterogeneity was assessed using Cochran’s Q test. A fixed-effect method was used in the absence of significant heterogeneity; the DerSimonian and Laird random-effects model used in the presence of significant heterogeneity.

The influence of risk status was examined by analysing separately low, intermediate and high risk groups (definitions of
risk groups were reported). Weighted linear regression was used to examine the relationship of radiotherapy dose to the percentage of patients with biochemical failure in five years.

Publication bias was assessed using a funnel plot, and the Begg-Mazumdar and the Egger's tests.

**Results of the review**

Seven RCTs were included (n=2,813 patients from tables; range 104 to 843).

High-dose radiotherapy was associated with a statistically significant reduction in biochemical failure compared with conventional-dose radiotherapy (OR 0.60, 99% CI 0.47 to 0.76; six RCTs; n=2,420 men). No significant heterogeneity was found. Low, intermediate and high risk groups all showed a significant reduction in biochemical failure with high-dose radiotherapy compared to conventional-dose radiotherapy.

There was no statistically significant difference between high-dose radiotherapy and conventional-dose radiotherapy in mortality (five RCTs; n=1,664 men) or prostate cancer-specific mortality (five RCTs; n=1,664 men). No significant statistical heterogeneity was found in either of these analyses.

In the text, the authors stated that high-dose radiotherapy was associated with a statistically significant increase in late Grade >2 gastrointestinal toxicity (OR 1.58, 99% CI 1.24 to 2.0; six RCTs; n=2,708 men), but reported no significant difference in late Grade >2 genitourinary toxicity (six RCTs; n=2,708 men). Forest plots showed that high-dose radiotherapy was associated with no statistically significant increase in Grade >2 gastrointestinal toxicity, but was associated with a significant increase in Grade >2 genitourinary (OR 1.59, 99% CI 1.25 to 2.01).

Meta-regression showed a linear correlation between radiotherapy dose and biochemical failure (biochemical failure = -67.3 + [1.8 times radiotherapy total dose in Gy]; p=0.04). Meta-regression also showed similar results across different risk groups.

There was no evidence of publication bias.

**Authors' conclusions**

High-dose radiotherapy was superior to conventional-dose radiotherapy in preventing biochemical failure in low, intermediate and high-risk men with localised prostate cancer, suggesting that high-dose radiotherapy should be offered to all such patients regardless of risk status.

**CRD commentary**

The review question was clearly stated and inclusion criteria were appropriately defined. Several relevant sources were searched, but it was not clear if attempts were made to minimise language bias. No attempts were made to minimise publication bias, but no evidence of this was found. Methods were used to minimise reviewer errors and bias in the selection of studies, but it was not clear whether similar steps were taken in study selection.

Only RCTs were included in the review, but validity was not assessed, so results from these trials and any synthesis may not be reliable. Little information was provided about the participants, treatment regimens or duration of follow-up. Appropriate methods were used for the meta-analyses and the influence of risk status and radiation dose was examined.

Evidence appeared to support the authors' conclusions, but incomplete reporting of review methods and lack of reporting of trial quality makes it difficult to comment on the strength or reliability of the evidence.

**Implications of the review for practice and research**

**Practice:** The authors stated that high-dose radiotherapy should be offered to all men with localised prostate cancer regardless of risk status.

**Research:** The authors stated that further studies are required to compare the delivery of radiotherapy doses greater than 80 Gy using image-guided radiotherapy and intensity-modulated radiotherapy.