Comparative evaluation of radiation treatments for clinically localized prostate cancer: an updated systematic review

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CRD summary
This review concluded that a lack of high-quality comparative evidence precluded conclusions being drawn about the efficacy of radiation therapies versus no treatment in the treatment of localized prostate cancer. This conclusion is likely to be reliable.

Authors' objectives
To review the clinical and biochemical outcomes of radiation therapies for localized prostate cancer.

Searching
MEDLINE and Cochrane Central Register of Controlled Trials (CENTRAL) were searched from 2007 to March 2011. Search terms were reported. Studies published before 2007 were identified using a previous review (see Other Publications of Related Interest). Only peer-reviewed studies published in full and reported in English were included.

Study selection
Randomised controlled trials (RCTs) and non-randomised comparative studies of first-line radiation therapy in men with clinically localised prostate cancer (T1 or T2, N0-X, M0-X) were included in the review.

Studies in which more than 20% of patients had locally advanced (T3 or T4) cancer were excluded. Also excluded were studies of adjuvant or salvage therapy, postprostatectomy radiation and studies that primarily evaluated androgen deprivation therapy in conjunction with radiation therapy. Radiation therapy was defined as including external beam radiation therapy, stereotactic body radiation therapy, brachytherapy, high-dose rate temporary brachytherapy and combinations thereof.

Comparators were no treatment or no initial treatment (active surveillance) and alternative radiation therapies. Outcomes assessed were overall survival, prostate cancer specific survival, metastases or clinical progression-free survival, biochemical failure, health status, quality of life and adverse events of grade 3 or higher.

Six reviewers independently assessed papers for inclusion in the review.

Assessment of study quality
Study validity was assessed using criteria of adequate power, randomisation, blinding, allocation concealment, use of intention-to-treat (ITT) analysis, length of follow-up, number of drop-outs and loss to follow-up. The evidence base for each comparison was rated as high, moderate or insufficient by all reviewers. Disagreements were resolved through consensus.

Data extraction
Data on outcomes at five years, 10 years and last reported time points were extracted to enable the calculation of risk or rate differences.

Data were extracted by one reviewer and checked by a second. Disagreements were resolved through consensus.

Methods of synthesis
The studies were combined in a narrative synthesis grouped by the comparison assessed.

Results of the review
Seventy-five studies (10 RCTs) were included in the review. The body of evidence for comparisons between external
beam radiation therapies was rated as moderate; evidence for all other comparisons was considered insufficient.

**Radiation therapy versus no treatment or no initial treatment (nine studies):** There were no RCTs and only one study was prospective; this involved modelling and reported a benefit of no treatment over external beam radiation therapy on sexual function and no differences between brachytherapy and no treatment. One of the four retrospective studies that assessed disease-specific survival reported a statistically significant benefit of brachytherapy over no treatment. Other outcomes assessed showed higher levels of adverse events in patients who received brachytherapy or external beam radiation therapy (three studies).

**Comparisons between radiation treatments (16 studies, six prospective):** Comparisons of low dose rate temporary brachytherapy with external beam radiation therapy showed inconclusive results for adverse effects outcomes, biochemical failure and disease-specific survival (one study). There was no statistically significant difference in any outcome in a retrospective comparison of high-dose and low-dose rate temporary brachytherapy (one study).

**Comparisons of combinations of radiation therapies (15 studies, two RCTs):** One RCT small found a benefit in biochemical or clinical failure rates at five years of external beam radiation therapy plus brachytherapy over external beam radiation therapy alone (adjusted hazard ratio 0.37, 95% confidence interval 0.16 to 0.85). The other RCT found no statistically significant difference in failure rate between low dose rate temporary brachytherapy plus external beam radiation therapy at two different doses. Non-randomised studies reported mixed results for biochemical failure, disease specific survival and adverse events.

**Comparisons within a given radiation treatment:** Intra-stereotactic radiation therapy (one retrospective study) showed no statistically significant differences in adverse events at two different doses. Intra-external beam radiation therapy (20 studies, seven RCTs and two other prospective studies). Fourteen studies (three RCTs and two other prospective studies) all found that high-dose external beam radiation therapy was associated with improved rates of freedom from biochemical failure after five to 10 years compared to lower dose therapy. No differences in bowel or urinary adverse events were found. There were no statistically significant differences on any outcome between standard fractionation and hypofractionation (six studies, four RCTs).

**Intra-low dose-rate temporary brachytherapy (three studies, one RCT):** The single RCT found no differences in biochemical failure or adverse events between iodine-125 and palladium-103. One retrospective study found that treatment dose was not associated with significant differences in adverse effects. The second study showed an improved overall survival rate and biochemical failure rate at higher doses of therapy.

**Authors’ conclusions**
A lack of high-quality comparative evidence precluded conclusions about the efficacy of radiation therapies compared with no treatments for localised prostate cancer.

**CRD commentary**
The review question and inclusion criteria were clear. Two relevant databases were searched. The decision to limit the review to published peer-reviewed studies reported in English may have introduced selection bias and omitted relevant studies. The authors used methods designed to reduce bias and error at all stages of the review process and conducted an appropriate validity assessment that was used to inform the synthesis. Use of a narrative synthesis was reasonable given the level of clinical heterogeneity between studies.

The authors’ conclusions reflected the limitations of the evidence base and appear likely to be reliable.

**Implications of the review for practice and research**
**Practice:** The authors did not state any implications for practice.

**Research:** The authors stated that there was a need for further research to evaluate external beam radiation therapy versus brachytherapy and the multiple dose and fractionation schedules in use. The authors stated that two ongoing RCTs to compare active surveillance with radical prostatectomy and radiation therapy (START and ProtecT trials) were expected to provide valuable data.
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