Comparative effectiveness of therapies for clinically localized prostate cancer
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CRD summary
The authors concluded that there was insufficient evidence to adequately compare the effectiveness and safety of interventions for clinically localised prostate cancer. There were limitations in the reporting of the review methods but, overall, the review was well conducted and presented and the authors’ conclusions are likely to be reliable.

Authors' objectives
To compare the effectiveness and harms of therapies for clinically localised prostate cancer, and to examine the effect of patient, tumour and treatment facility characteristics on the outcomes. This abstract focuses on effectiveness and harms.

Searching
Randomised controlled trials (RCTs) were sought using the Cochrane Library and the specialised register of the Cochrane Prostatic Diseases and Urologic Cancers Group through September 2007. MEDLINE was searched from 2000 to September 2007 for studies reported in the English language; the search terms were provided. In addition, the results from an existing database containing mainly non-randomised studies, which was used for the Guidelines for the Management of Clinically Localized Prostate Cancer: 2007 update (PubMed search between 2001 and April 2004; (see Other Publications of Related Interest no.1), were also considered. Additional data on harms and patient satisfaction were obtained from the Prostate Cancer Outcomes Study (see Other Publications of Related Interest no.2) and the National Cancer Institute's Surveillance Epidemiology and End Results Program. Further articles were identified through contact with Endocare (a manufacturer).

Study selection
RCTs that evaluated any treatment for prostate cancer in men considered to have clinically localised disease (tumour stage T1 or T2), regardless of age, histologic grade or prostate-specific antigen (PSA) level, were eligible for inclusion. RCTs that reported data separately for this subgroup of patients were also included. Studies in the pre-existing American Urological Association database were only included if the sample size was 100 or more and the results were presented separately for patients with localised disease. Since no RCTs of emerging treatments were identified, non-randomised trials, reviews and case series of these treatments were included.

The review evaluated a variety of treatments including radical prostatectomy with and without androgen deprivation therapy, watchful waiting, and different types of external beam radiotherapy (EBRT) with and without androgen deprivation treatment and brachytherapy.

The authors stated that 'decisions of study eligibility were made with no relation to authors' but provided no further information about the study selection process.

Assessment of study quality
The quality of RCTs was assessed using allocation concealment, intention-to-treat analysis, length of follow-up, and drop-outs or losses to follow-up. The quality of the evidence for each intervention was estimated using U.S. Preventive Services Task Force criteria and the Agency for Healthcare Research and Quality scale (high, medium or low).

It was unclear whether or not the validity assessment was performed in duplicate.

Data extraction
Two reviewers independently extracted the data onto a standardised form. Standard errors, regression coefficients and 95% confidence intervals (CIs) were calculated from reported data where possible.

Methods of synthesis
The studies were grouped by design (RCT and other) and intervention and generally combined in a narrative, with accompanying tables. Where comparable studies provided sufficient data, pooled absolute risk differences with 95% CIs were calculated using a random-effects model, and statistical heterogeneity was assessed using the $\chi^2$ and $I^2$ statistics. The influence of the following factors on treatment outcomes was discussed: patient characteristics; clinical setting; length of follow-up and adjustment for confounding.

Results of the review
Eighteen RCTs and one pooled analysis of 3 trials (n=14,595) and 473 observational studies were included.

No intervention was supported by consistent results from two high-quality, adequately powered RCTs with adequate follow-up.

Limitations in the identified evidence included a paucity of studies directly comparing major treatments, underpowered RCTs, failure to report long-term survival rates, RCTs conducted in the era before PSA testing, wide variation in the reporting and definitions of outcomes, and failure to report the results stratified by patient and tumour characteristics.

No RCTs evaluated cryotherapy, laparoscopic- or robotic-assisted radical prostatectomy, primary androgen deprivation, high-intensity focused ultrasonography, proton beam radiation or intensity-modulated radiation therapy.

There were 2 RCTs of radical prostatectomy versus watchful waiting. The larger RCT (n=695 men, most without PSA-detected disease) reported that radical prostatectomy reduced all-cause deaths (24% versus 30%, $p=0.04$) and disease-specific deaths (10% versus 15%, $p=0.01$) at 10 years, but increased urinary and sexual dysfunction compared with watchful waiting. The smaller, older RCT (n=142) reported no significant difference between treatments in overall survival.

One small, older RCT (n=106) reported that radical prostatectomy was associated with reduced disease recurrence compared with EBRT (14% versus 39%, $p=0.04$).

The addition of neoadjuvant androgen deprivation therapy to radical prostatectomy was not associated with any improvement in survival or cancer recurrence rates, but was associated with an increase in adverse events (3 RCTs).

None of the EBRT regimens appeared to be better than any other at reducing overall or disease-specific mortality (5 RCTs).

Androgen deprivation treatment plus EBRT may reduce overall and disease-specific mortality, but it increased adverse events compared with EBRT alone in high-risk patients (3 RCTs).

The non-randomised studies were predominantly case series. Definitions of adverse events varied considerably. It was not possible to compare treatments in terms of their efficacy or adverse events.

Many other results were also reported.

Authors' conclusions
There was insufficient evidence to adequately compare the effectiveness and safety of interventions for clinically localised prostate cancer.

CRD commentary
The review question was stated clearly. Several relevant sources were searched. Attempts were made to minimise publication bias, but not language bias, so other relevant studies could have been missed. Appropriate methods were used to minimise reviewer error and bias during the data extraction process, but it was unclear whether similar methods were used when selecting studies and assessing their validity. The quality of the included studies was assessed, and the results reported and taken into account when drawing conclusions. A predominantly narrative synthesis, with studies grouped by design and intervention, was appropriate given the diversity of the studies. There were limitations in the reporting of the review methods but, overall, the review was well conducted and presented and the authors’ conclusions are likely to be reliable.
Implications of the review for practice and research

Practice: The authors stated that limitations in the currently available evidence mean that no single treatment can be considered the preferred for localised prostate cancer.

Research: The authors stated the need for long-term, adequately powered RCTs to compare different treatments for localised prostate cancer. Studies need to assess standardised outcomes and ideally stratify results according to patient and tumour characteristics. Future research questions could be identified by analysing data from large prospective cohort studies or cancer registries. There is also a need to identify biochemical markers of the aggressiveness of prostate cancers that could be used to compare treatments. Educational materials that provide patients with information about the risks and benefits of treatments are required.

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the reliability of the review and the conclusions drawn.