The role of androgen deprivation in the definitive management of clinically localized prostate cancer treated with radiation therapy

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Authors' objectives
To determine the efficacy of androgen deprivation given in combination with radiotherapy for localised prostate cancer and the patients most suitable for its application.

Searching
MEDLINE was searched from January 1980 to September 1998 for English language studies. The keywords employed were stated in the paper.

Study selection
Study designs of evaluations included in the review
Studies on prostate cancer treatment employing radiotherapy combined with androgen deprivation were included. Study designs include both retrospective studies and prospective randomised controlled trials (RCTs). Median follow-up ranged from 22 to 174 months.

Specific interventions included in the review
The following regimes of androgen deprivation used in conjunction with radiotherapy were compared with radiotherapy alone: luteinizing hormone releasing hormone with or without antiandrogens; estrogen; cryptoterone; DES; castration; megace; goserelin; and variable regimes, including complete androgen deprivation (CAD). Androgen deprivation was given both pre and post radiotherapy. Radiotherapy doses ranged from 60 to 79 Gy.

Participants included in the review
Patients with variable stages and grades of localised prostate cancer were studied.

Outcomes assessed in the review
Indicators of local, regional and biochemical control were assessed including biopsy results, disease free survival, and overall survival.

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the authors performed the selection.

Assessment of study quality
Studies were grouped into two categories according to study design (prospective RCT and retrospective reports). The following aspects of validity were considered though no formal assessment was reported: baseline comparability; interventions; outcomes; details of radiotherapy; and follow-up period.

Data extraction
A comprehensive data extraction form was designed to review each article.

Methods of synthesis
How were the studies combined?
The studies were combined in a narrative review.

How were differences between studies investigated?
Differences between studies were considered in the narrative.

Results of the review
Fourteen retrospective studies (1599 patients) and 6 RCTs (2289 patients) were included.

Significant results were indicated in the tables by bold numbers which were not always easy to differentiate from non-bold printed results. No level was reported for classifying results as statistically significant. The abbreviation DMFS was used as an outcome without definition.

Differences in study design included the following: unequal distributions of pre-treatment prognostic factors including stage, grade, and prostate specific antigen levels; substantial variability in the type, duration, and timing of hormonal manipulation; significantly different end points used to judge efficacy; variable total dose and technique of radiotherapy; and large differences in median follow-up.

Retrospective studies. Local control (4 studies): results inconsistent with 2 studies reporting no significant difference between group and 2 favouring androgen suppression. Disease free survival (6 studies): results inconsistent with 4 studies reporting no significant difference and 2 favouring androgen suppression. DMFS (6 studies): results inconsistent with 6 studies reporting no significant difference and 1 favouring androgen suppression. Overall survival (7 studies): results inconsistent with 5 studies reporting no significant difference and 2 favouring androgen suppression. Biochemical control (4 studies): results inconsistent with 1 study reporting no significant difference and 3 favouring androgen suppression.

RCTs: Local control (5 studies): results inconsistent with 1 study reporting no significant difference and 4 favouring androgen suppression. Disease free survival (4 studies): results inconsistent with 2 studies reporting no significant difference and 2 favouring androgen suppression. DMFS (3 studies): all 3 favoured androgen suppression. Overall survival (5 studies): results inconsistent with 4 studies reporting no significant difference and 1 favouring androgen suppression. Biochemical control (4 studies): results consistent with all 4 favouring androgen suppression. Cancer specific survival (1 study): no significant difference.

Authors' conclusions
No definite conclusions could be reached on the impact on overall survival and cancer specific survival of androgen withdrawal given in combination with radiotherapy. However, local/regional control, disease free survival and biochemical control were almost uniformly improved with the use of androgen withdrawal suggesting that these impressive early results may translate into improved cure rates. Data from recently initiated and completed randomised trials will be needed to define the impact of this approach on cancer specific mortality and the patients most suitable for its use.

CRD commentary
The aims and inclusion criteria were stated. Some relevant details of primary studies were presented in tabular format. Given the differences between studies a narrative review was appropriate. Aspects of validity were discussed and variability between studies highlighted. The discussion included consideration of the following: difficulty in comparing and contrasting results from individual studies due to problems associated with defining an appropriate end point; lack of consistent pre-stratification of patients by prognostic factors; possibility of under detection of cancer cells as a result of morphological changes induced by androgen ablation; degree of correlation of pathological findings with clinical outcome; and problems with the accuracy of defining disease status in patients at the time of death. By limiting the literature search to articles published in the English language and identified in MEDLINE, some other relevant studies may have been omitted. The inclusion criteria do not include consideration of methods of ascertainment of the diagnosis of prostate cancer and no details were given of methods used to determine outcomes in the primary studies. No details were given of methods used to select primary studies, assess validity or extract data. Any heterogeneity among studies could have been demonstrated graphically or by calculating difference rates and 95% confidence intervals for reported outcomes of primary studies. It was not clear whether results for the RCTs were reported as intention to treat.
Given the lack of definition of participants and outcomes, heterogeneity among results and the problems of research to date in this field discussed by the author, any conclusion from the evidence is rightly cautious.

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

Practice: The authors do not report any clinical implications from the review.

Research: The authors mention some either recently completed or ongoing studies in this area for which results are not yet available and suggest that future studies should address the problem of defining disease status in patients at the time of death.

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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.