Long-term hormone therapy and radiation is cost-effective for patients with locally advanced prostate carcinoma
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Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
The study examined long-term androgen-deprivation (LTAD) and short-term androgen-deprivation (STAD). Both treatments were given together with radiotherapy (RT) for the treatment of patients with adenocarcinoma of the prostate. All patients received flutamide at a dose of 250 mg orally 3 times daily, with monthly goserelin acetate (3.6 mg subcutaneously) beginning 2 months prior to RT and continuing until RT was completed. Patients in the STAD arm received no further treatment, whereas patients in the LTAD arm received monthly injections of goserelin (3.6 mg subcutaneously) for an additional 2 years after the completion of RT.

Type of intervention
Treatment.

Economic study type
Cost-utility analysis.

Study population
The study population comprised men with histologically confirmed adenocarcinoma of the prostate.

Setting
The setting was a hospital. The economic study was carried out in the USA.

Dates to which data relate
The effectiveness data were derived from studies published between 1996 and 2003. Resource consumption was obtained from a clinical trial published in 2003. Some costs were derived from a study published in 2002. The price year was not reported.

Source of effectiveness data
The effectiveness evidence was derived from a synthesis of published studies.

Modelling
A Markov model was set up to assess the costs and benefits of LTAD versus STAD in a cohort of patients with locally advanced prostate carcinoma. The time horizon of the model was 10 years and the cycle length was 1 year. The health states considered in the model were no disease progression, hormone-responsive disease progression, hormone-unresponsive disease progression and death. The allowable state transitions were from no disease progression, to hormone-responsive disease progression, to hormone-unresponsive disease progression, to death. The transitions from states of no disease progression to states of hormone-responsive and hormone-nonresponsive disease progression were biochemical determinations. Only forward transitions were allowed.
Outcomes assessed in the review
The outcomes estimated from the literature were:

disease-free survival,

the annual probabilities of dying, biochemical failure, gastrointestinal (GI) toxicity and progression after initial hormone therapy,

the utility values associated with specific health states, and

the utility decrements for dysfunction.

The annual transition probabilities were also estimated for a sub-group of patients with a Gleason score of at least 8 (high-risk patients).

Study designs and other criteria for inclusion in the review
It was unclear whether the authors performed a systematic review of the literature. The primary studies appear to have been identified selectively. Most of the data came from the Radiation Therapy Oncology Group (RTOG) clinical trial. The utility values were estimated from a sample of 95 patients with prostate carcinoma.

Sources searched to identify primary studies
Not reported.

Criteria used to ensure the validity of primary studies
The use of a randomised clinical trial ensures a high internal validity of the source used to derive transition probabilities.

Methods used to judge relevance and validity, and for extracting data
Not reported.

Number of primary studies included
Five primary studies provided the clinical data.

Methods of combining primary studies
Not reported.

Investigation of differences between primary studies
Not reported.

Results of the review
The 5-year disease-free survival rate was 28.1% for patients who received STAD and 46.4% for patients who received LTAD.

No difference was observed in overall survival between the STAD group and the LTAD group.

Patients who exhibited a biochemical failure after LTAD had a worse progression-free survival than patients who initially received STAD.
The annual rate of death was 0.0472 with STAD and 0.045 with LTAD.

The annual rate of biochemical failure was 0.22 with STAD and 0.145 with LTAD.

The annual rate of GI toxicity was 0.002 with STAD and 0.005 with LTAD.

The annual rate of progression after initial hormone therapy was 0.046 with STAD and 0.09 with LTAD.

The differences in annual rates between the groups were not statistically significant.

In the sub-group of patients with a Gleason score of at least 8:

the annual rate of death was 0.067 with STAD and 0.041 with LTAD,

the annual rate of biochemical failure was 0.28 with STAD and 0.15 with LTAD,

the annual rate of GI toxicity was 0.002 with STAD and 0.005 with LTAD, and

the annual rate of progression after initial hormone therapy was 0.046 with STAD and 0.09 with LTAD.

The utility values were 0.749 for RT and androgen deprivation, 0.793 for androgen deprivation, and 0.420 for chemotherapy.

The utility decrements for dysfunction were 0.08 to 0.14 (sexual), 0.06 to 0.13 (urinary), and 0.01 to 0.13 (bowel).

**Measure of benefits used in the economic analysis**
The summary benefit measure used was the number of quality-adjusted life-years (QALYs). QALYs were estimated by combining utility and survival data that were derived from the literature. An annual discount rate of 3% was applied.

**Direct costs**
The analysis was carried out from the perspective of the health care payer. It included the costs of androgen-deprivation and RT, hormone treatment after biochemical failure, and treatment in the last year of life. The unit costs were not presented separately from the quantities of resources used. Resource use consumption was based on data derived from the RTOG study. Most of the costs were obtained from Medicare rates. The mean cost of all therapies for the last year of life for a patient with metastatic prostate carcinoma was obtained from a study published in 2002. Discounting was relevant, owing to the long timeframe of the analysis, and an annual rate of 3% was applied. The price year was not reported.

**Statistical analysis of costs**
The costs were sampled using a normal distribution, with the cost used as the mean and a standard deviation that was 60% of the calculated cost.

**Indirect Costs**
The indirect costs were not included in the economic evaluation.

**Currency**
US dollars ($).

**Sensitivity analysis**
One- and two-way sensitivity analyses were carried out to assess the robustness of the cost-effectiveness ratios to
variations in selected clinical and economic inputs. The sources of the alternative ranges of values were not reported. A probabilistic sensitivity analysis was also performed using a Monte Carlo simulation with 1,000 trials. Cost-effectiveness acceptability curves were then generated. The utility values and transition probabilities were assumed to have beta distributions, while the costs were assumed to be distributed normally. In an alternative analysis a gamma distribution was used for the costs.

**Estimated benefits used in the economic analysis**
The expected QALYs were 3.68 for patients in the STAD arm and 4.13 for patients in the LTAD arm.
The corresponding values in the sub-group of high-risk patients were 3.48 (STAD) and 4.16 (LTAD).

**Cost results**
The expected mean costs were $33,059 for patients in the STAD arm and $32,564 for patients in the LTAD arm.
The corresponding values in the sub-group of high-risk patients were $28,688 (STAD) and $31,820 (LTAD).

**Synthesis of costs and benefits**
An incremental analysis was performed to combine the costs and QALYs in a cost-utility ratio.

LTAD dominated STAD, which was less effective and more expensive. The cost-effectiveness acceptability curve showed that LTAD had a 91% probability of being cost-effective in comparison with STAD at the willingness-to-pay level of $50,000 per QALY.

In the sub-group of high-risk patients, the incremental cost per QALY gained with LTAD in comparison with STAD was $4,605. The cost-effectiveness acceptability curve showed that LTAD had a 95.6% probability of being cost-effective at the willingness-to-pay level of $50,000 per QALY.

The sensitivity analysis suggested that LTAD remained cost-effective even with a shorter time horizon. For example, when the model was limited to 5 years, the incremental cost per QALY was $35,125. A similar conclusion was reached when the assumption of normal distribution of costs was released. Assuming an increased GI toxicity in patients receiving LTAD, the incremental cost per QALY was $47,333.

A threshold analysis, in which all probabilities and utilities were varied within reasonable ranges, demonstrated that LTAD remained the most cost-effective strategy except when the probability of disease progression in patients receiving LTAD was increased above 0.22. Changes in the costs did not alter the conclusions of the analysis.

**Authors’ conclusions**
Despite increased toxicity and costs, long-term androgen-deprivation (LTAD) in men with locally advanced prostate cancer was cost-effective in comparison with short-term androgen-deprivation (STAD).

**CRD COMMENTARY - Selection of comparators**
The authors justified the choice of the comparators, which were appropriate given the objectives of the study. The dosages were clearly reported. The authors stated that other interventions, such as orchietomy or medical castration, might be cheaper but they were not considered since the effect is permanent. You should decide whether they are valid comparators in your own setting.

**Validity of estimate of measure of effectiveness**
The effectiveness data were obtained from published studies. These studies were presumably identified selectively rather than by means of a systematic review of the literature. Most of the clinical evidence was derived from a randomised clinical trial, which should have ensured a high internal validity. Therefore, the population of the study
reflected the patients included in the RTOG study. Published studies were also used to derive the utility values, which were elicited from a sample of patients. Several sensitivity analyses were performed to assess the impact of variations in clinical estimates on the results of the analysis.

Validity of estimate of measure of benefit
The use of QALYs as the summary benefit measure was appropriate since QALYs capture the impact of the interventions on the two most relevant dimensions of health for patients with prostate carcinoma (i.e. survival and quality of life). Discounting was performed, as recommended by guidelines for economic evaluations in the USA. The sources of the utility adjustments were reported.

Validity of estimate of costs
The analysis of the costs was consistent with the perspective adopted in the study, and the costs included were appropriate. The costs were not broken down and were presented as macro-categories. Consequently, information on the unit costs and quantities of resources used was not presented clearly, which could limit the possibility of replicating the analysis in other settings. The source of the data was given but the price year was not, which makes reflation exercises in other time periods difficult. Statistical analyses of the costs were carried out and specific cost categories were varied in the sensitivity analysis.

Other issues
The authors reported the results from other economic evaluations of LTAD, which appeared to confirm the current findings. The issue of the generalisability of the study results to other settings was not explicitly addressed, although the use of a probabilistic sensitivity analysis corroborated the robustness of the base-case results. The study referred to men with histologically confirmed adenocarcinoma of the prostate and this was reflected in the authors' conclusions.

Implications of the study
The study results support the use of LTAD for the treatment of patients with prostate adenocarcinoma. The study showed that the increased cost and added toxicity are justified because QALYs are increased by the prevention of future biochemical failures.

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