Is proton beam therapy cost effective in the treatment of adenocarcinoma of the prostate?
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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 proton beam therapy and intensity-modulated radiation therapy (IMRT) for the treatment of prostate cancer.

Type of intervention
Treatment.

Economic study type
Cost-utility analysis.

Study population
The study population comprised a hypothetical cohort of male patients diagnosed with intermediate-risk adenocarcinoma of the prostate. The typical age of the cohort was 70 years (the age of 60 years was also considered in the sensitivity analysis).

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

Dates to which data relate
The clinical data were derived from studies published in 2003 and 2007. No dates for resource use were reported. The price year was 2005.

Source of effectiveness data
The clinical estimates included:

- transition probabilities between health states used in the decision model,
- death rates in different health states, and
- the 5-year probability of freedom from biochemical failure (FFBF) for patients treated with proton beam therapy or IMRT.

Modelling
A Markov model was used to determine the costs and benefits of the two strategies under examination. The time horizon of the model was 15 years, with annual cycles. A schematic representation of the model was reported. The health states included in the model were clearly described and were post-treatment, disease progression hormonally responsive (hormone therapy), disease progression hormonally unresponsive (chemotherapy) and death. It was assumed that patients spent 1 year in the chemotherapy cycle before dying.
Sources searched to identify primary studies
Transition probabilities and FFBF rates were derived from two key published studies, no details of which were reported. Age- and gender-related survival was obtained from published life tables.

Methods used to judge relevance and validity, and for extracting data
The published studies appear to have been identified selectively rather than through a systematic review of the literature. The authors used standard formulae to calculate the annual transition probabilities used in the model. The authors picked the existing clinical data for the highest dose of IMRT.

Measure of benefits used in the economic analysis
The summary benefit measure used was the quality-adjusted life-years (QALYs). These were calculated using the Markov model. The utility weights required to adjust expected survival were based on different sources, such as a sample of patients interviewed by the authors in a clinical trial (for utility values associated with IMRT and proton beam therapy) and published studies (for utility values associated with hormone therapy and chemotherapy). The utility weights for patients interviewed by the authors were obtained using the EuroQol at five dimensions (EQ-5D). An annual discount rate of 3% was applied to benefits accruing in the future.

Direct costs
The analysis of the costs was carried out from the perspective of the reimbursement authority, namely Medicare. It included the costs associated with IMRT, proton beam therapy, hormone therapy and chemotherapy. A breakdown of the cost items was not provided. However, the authors stated that the main categories of costs were technical (hospital) components of treatment, physician services, hormone therapy, and all therapies (including chemotherapy) associated with terminal care. The costs were derived from ambulatory payment classification payment rates for the technical aspects and from resource-based relative value units for physician services. The costs of hormone therapy came from average wholesale prices obtained from the Drug Red Book. The costs of terminal care came from a published study. Information on resource consumption was not reported clearly. Discounting was relevant, as the long-term costs were considered, and an annual rate of 3% was used. The price year was 2005.

Statistical analysis of costs
The costs were assumed to have been normally distributed and sampled once per patient.

Indirect Costs
Productivity costs were not included in the analysis.

Currency
US dollars ($).

Sensitivity analysis
The issue of uncertainty was addressed in a probabilistic sensitivity analysis (second-order Monte Carlo simulation) in which costs, transition probabilities and utility weights were varied according to stochastic distributions. Individual assumptions regarding the most uncertain model inputs were also tested using univariate sensitivity analysis. A net monetary benefit was also calculated and acceptability curves were presented.

Estimated benefits used in the economic analysis
The 15-year expected QALYs were 8.54 with proton beam therapy and 8.12 with IMRT in a 70-year-old patient. The corresponding QALYs in a 60-year-old patient were 9.91 and 9.45, respectively.
Cost results
The 15-year expected costs were $63,511 with proton beam therapy and $36,808 with IMRT in a 70-year-old patient. The corresponding figures in a 60-year-old patient were $64,989 and $39,355, respectively.

Synthesis of costs and benefits
Incremental cost-utility ratios were calculated in order to combine the costs and benefits of the two strategies.

The 15-year model led to an incremental cost per QALY gained of $63,578 with proton beam therapy in comparison with IMRT in a 70-year-old man ($55,726 in a 60-year-old man).

The probabilistic sensitivity analysis showed that, in a 70-year-old man, proton beam therapy had only a 49% probability of being cost-effective (cost per QALY below the threshold of $50,000) at 15 years. Furthermore, as regards cost assumptions, proton beam therapy would have a higher net monetary benefit compared with IMRT if the costs of IMRT were more than $45,000 (base-case $25,846), the costs of proton beam therapy were less than $39,000 (base-case $58,610) or the utility associated with IMRT was lower than 0.85 (0.9 in the base-case). Slightly better results for proton beam therapy were achieved in a younger patient (the probability for proton beam therapy of being cost-effective given a threshold of $50,000 per QALY was 54%).

Authors’ conclusions
Proton beam therapy for patients with prostate cancer was not a cost-effective strategy in comparison with intensity-modulated radiation therapy (IMRT) given the currently used threshold of $50,000 per quality-adjusted life-year (QALY). The results of the analysis suggested that only younger patients with longer life expectancy might benefit from proton beam therapy in an efficient manner.

CRD COMMENTARY - Selection of comparators
The choice of the comparators reflected the treatments available for prostate cancer, with proton beam therapy having clinical advantages over conventional IMRT. The highest dose for IMRT was chosen. You should decide whether they are valid comparators in your own setting.

Validity of estimate of measure of effectiveness
The clinical inputs were derived from two key published studies. However, details of both these primary sources and the approach used to identify them were not provided. Furthermore, the authors did not justify their choice of these data and did not explain how the primary estimates were selected. Thus, it is difficult to assess the validity of the clinical data. However, the issue of uncertainty surrounding these parameters was investigated in the sensitivity analysis.

Validity of estimate of measure of benefit
Benefits (i.e. QALYs) were estimated using a modelling approach. Appropriate discounting was applied, in accordance with US guidelines. The use of QALYs was appropriate given the nature of disease since they capture the impact of the treatments on both quality of life and survival. The sources and instruments used to obtain the utility weights were extensively described and the choice of these estimates was justified.

Validity of estimate of costs
The costs included were consistent with the perspective adopted in the study. However, limited information on the unit costs and resource quantities was provided. Furthermore, the costs were presented as macro-categories and were not broken down into individual items. The sources of the costs were appropriate given the viewpoint of the analysis. In effect, typical Medicare sources were used to derive the costs. No information on resource use was provided, which limits the possibility of replicating the analysis in other settings.

Other issues
The authors made some comparisons of their results with the findings from other studies, in particular in terms of clinical results. The issue of the generalisability of the study results to other settings was not explicitly addressed, but
the use of probabilistic sensitivity analysis enhances the external validity of the study. It should be noted that, although the authors concluded that proton beam therapy was not cost-effective, the cost-effectiveness ratios were actually quite close to the threshold of $50,000 and small variations in some parameters (e.g. utility weights) might change the conclusion of the analysis. In general, there is high uncertainty around the cost-effectiveness results, as shown by the acceptability curves. The authors provided an extensive discussion of the role played by radiation dose in their analysis.

Implications of the study
The study results do not support the widespread use of proton beam therapy for the treatment of prostate cancer. The authors recommend the conduct of well-designed clinical trials in order to provide a better evaluation of the cost-effectiveness of proton beam therapy in prostate cancer.

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