Proton therapy of cancer: potential clinical advantages and cost-effectiveness
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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 use of proton beam therapy for the treatment of patients with one of four types of cancer: left-sided breast cancer (BC), prostate cancer (PC), head and neck cancer (HNC) and medulloblastoma (MB).

Type of intervention
Treatment.

Economic study type
Cost-utility analysis.

Study population
The study population comprised hypothetical cohorts of patients, each with one of the four types of cancer considered in the analysis. The cohorts were patients with PC and HNC aged 65 years or more, patients with BC aged 55 years or more, and children with MB aged 5 years or more.

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

Dates to which data relate
The effectiveness and resource use data were derived from studies published between 1992 and 2005. The price year was 2002.

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

Modelling
Four identical Markov models were used to assess the clinical and economic impact of proton therapy, compared with conventional radiotherapy, for the treatment of hypothetical patients with cancer. The time horizon of the model was a patient's lifetime, and the cycle length was one year. The two main arms of the decision tree (conventional versus proton therapy) were identical. After treatment, patients could be healthy, experience adverse event conditions, or die. Healthy patients could experience no complications, die, or experience fatal or nonfatal adverse events. Patients experiencing adverse events could survive or die. Death was related to cancer, adverse events, or all-cause mortality. A graphical representation of the model was provided.

Outcomes assessed in the review
The outcomes estimated from the literature were:
the probabilities of adverse events related to proton therapy;

the rates of death;

the efficacy of proton therapy versus conventional radiation (expressed as relative risk, RR); and

health utility reductions associated with adverse events.

**Study designs and other criteria for inclusion in the review**
The authors identified primary studies used as the source of clinical data from a systematic review of the literature, but details of the review were not reported. Little information on the design, sample size and other characteristics of these studies was provided. Many studies were performed in the Swedish context.

**Sources searched to identify primary studies**
Not reported.

**Criteria used to ensure the validity of primary studies**
Not reported.

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

**Number of primary studies included**
Approximately 50 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**
For BC patients, in comparison with the general population, the increased risk of ischaemic heart disease was 43%, the increased risk of other cardiovascular disease was 27%, and the annual risk of pneumonitis was 14%. The utility reduction associated with ischaemic heart disease was 10%, and 20% for other cardiovascular disease. The RR of ischaemic heart disease, other cardiovascular disease or pneumonitis with proton therapy versus conventional radiation was 0.24.

For PC patients, the rate of PC death for 15 years was 2.5%. The annual probability of mild gastrointestinal adverse events was 14%, the annual probability of severe gastrointestinal adverse events was 4%, the annual probability of mild urogenital adverse events was 9%, and the annual probability of severe urogenital adverse events was 0.5%. The RR of PC-related death (proton therapy versus conventional therapy) was 0.8, while the RR of adverse events was 0.6. The utility reduction associated with adverse events was 7%.

The mortality rate associated with HNC was 16% for 8 years and the RR of death (proton therapy versus conventional therapy) was 0.76.

For children with MB, the rate of death due to subsequent cancer was 0.11% and the rate of death due to cardiac
disease and other deaths was 0.056%. The probability of hearing loss was 13%, the IQ loss was 4.25 points, the probability of hypothyroidism was 33%, the probability of growth hormone deficiency was 18.7%, and the probability of osteoporosis was 2.4%. The rate of nonfatal cancers was 0.32%. The RR (proton therapy versus conventional therapy) was 0.48 for death due to subsequent cancer, 0.77 for death due to cardiac disease and other deaths, and 0.12 for other events. The utility reduction was 18% for hearing loss, 10% during one year for hypothyroidism, 20% for growth hormone deficiency, and 2% for osteoporosis.

Measure of benefits used in the economic analysis
The summary benefit measure used was the total number of quality-adjusted life-years (QALYs) associated with proton therapy in comparison with conventional treatment. The QALYs were estimated by combining, in the decision model, survival data and utility weights obtained from the literature. An annual discount rate of 3% was applied.

Direct costs
The perspective used in the analysis was not explicitly stated, but the main costs were those associated with proton therapy and conventional treatment, and the treatment of adverse events associated with therapy. With respect to radiotherapy, the three main cost categories considered were operation costs, capital costs, and travel and/or hotel costs. Some details on the calculation of the radiotherapy costs were reported, but information on resource consumption and unit costs associated with side effects was not given. The proportion of patients requiring travel and transportation costs was based on authors' assumptions. Most estimates came from published studies. Swedish sources were used for the unit costs. Discounting was relevant as long-term costs were evaluated, and an annual rate of 3% was applied. The price year was 2002, and the cost estimates for previous years were updated to 2002 values using the Swedish Consumer Price Index.

Indirect Costs
The indirect costs were not considered.

Currency
Euros (EUR). The exchange rate from Swedish kroners (SEK) was EUR 1 = SEK 9.2.

Sensitivity analysis
Several deterministic analyses were carried out, although the authors did not report extensive information on the way the issue of uncertainty was dealt with. Several model inputs, including risk of treatment side effects, radiotherapy costs and efficacy of proton therapy, were varied in the univariate sensitivity analyses.

Estimated benefits used in the economic analysis
Under the base-case assumptions, the additional QALYs gained with proton therapy versus conventional radiotherapy were 0.1726 for BC (high-risk individuals), 0.297 for PC, 1.02 for HNC and 0.683 for MB.

Cost results
Under the base-case assumptions, the additional costs associated with proton therapy versus conventional radiotherapy were EUR 5,920 for BC, EUR 7,952.6 for PC, EUR 3,887.2 for HNC and EUR -23,646.5 for MB.

Synthesis of costs and benefits
Incremental cost-utility ratios were calculated to combine the costs and QALYs of proton therapy versus conventional therapy.

The incremental cost per QALY was EUR 34,290 for BC, EUR 26,776 for PC and EUR 3,811 for HNC. The incremental analysis revealed that proton radiation dominated conventional treatment for patients with MB.

Assuming a facility treated 300 patients with BC (population at high-risk of cardiac disease), 300 patients with PC, 300 patients with HNC and 25 cases of MB every year, the incremental cost per QALY gained per average patient with proton therapy in comparison with conventional radiotherapy was EUR 10,130.

The sensitivity analysis suggested that the cost-utility estimates were sensitive to variations in probability and cost estimates, given the great uncertainty surrounding some model inputs. However, proton therapy for MB was always a dominant strategy, regardless of variations in clinical estimates. The risk of cardiac disease in BC patients and the effect of proton therapy on PC patients and HNC patients were the most influential model inputs. If the value of a QALY gained was EUR 55,000 (the threshold for cost-effectiveness adopted in Sweden), the total yearly net benefit in Sweden of using proton therapy instead of standard therapy would be about EUR 20.8 million.

Authors' conclusions
The study results suggested that proton therapy was a cost-effective treatment strategy for several groups of high-risk patients with breast cancer (BC), prostate cancer (PC), head and neck cancer (HNC), or medulloblastoma (MB) in Sweden.

CRD COMMENTARY - Selection of comparators
The authors justified their choice of the comparator, which represented the latest technology, whenever possible. The study focused on these four types of cancers because proton therapy has already been shown to be cost-effective for other types of cancers. You should decide whether they are valid comparators in your own setting.

Validity of estimate of measure of effectiveness
The effectiveness data used to populate the decision model were obtained from published studies. The authors stated that the literature was searched to identify these studies, but the methods and conduct of a systematic review were not reported. Further, limited information on the design of the primary studies was provided and details of patient samples and follow-up were not given. Therefore, it was difficult to assess the validity of the primary sources. The issue of heterogeneity among the primary estimates was not investigated. The issue of uncertainty was partially addressed in the deterministic sensitivity analysis.

Validity of estimate of measure of benefit
QALYs were the most appropriate benefit measures because they capture the impact of the interventions on both quality of life and survival, which are the most relevant dimensions of health for patients with cancer. Little information on the sources of the utility weights was provided. QALYs can be compared with the benefits of other health care interventions. Discounting was applied, as recommended in economic evaluation guidelines.

Validity of estimate of costs
The authors did not state explicitly which perspective was chosen for the analysis. A detailed breakdown of the costs was not provided since most costs were presented as macro-categories. This might limit the possibility of replicating the cost analysis in other settings. The sources of data were reported for all costs, although few details of these studies were provided. Discounting was relevant and was appropriately applied. The price year was reported, which will facilitate reflation exercises in other time periods. The costs were not treated stochastically, and only macro-categories were varied in the sensitivity analysis.
Other issues
The authors did not compare their findings with those from other studies. They also did not address the issue of the generalisability of the study results to other settings. Some sensitivity analyses were carried out, but they were directed towards assessing the impact of individual model inputs. The authors pointed out the lack of published evidence on treatment efficacy and several economic aspects associated with the use of proton therapy in patients with cancer. Therefore, some model inputs were very uncertain. For example, the analysis relied on an assumed lifetime of 30 years for the proton therapy facility, although the availability of more advanced equipment would reduce the strength of this assumption.

Implications of the study
The study results suggest that proton therapy could represent an efficient use of resources for patients with specific types of cancer such as BC, PC, HNC and MB. However, the authors pointed out that caution will be required when interpreting the results of the study, given the uncertainty in some model assumptions.

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Other publications of related interest


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MeSH
Aged; Child, Preschool; Cohort Studies; Computer Simulation; Cost-Benefit Analysis; Female; Health Care Costs /statistics & numerical data; Humans; Male; Middle Aged; Models, Economic; Neoplasms /economics /radiotherapy; Protons /therapeutic use; Quality-Adjusted Life Years; Radiotherapy /economics; Sweden