**Decision-analytic model and cost-effectiveness evaluation of postmastectomy radiation therapy in high-risk premenopausal breast cancer patients**

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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 postmastectomy radiation therapy (PMRT) in high-risk breast cancer patients was studied.

**Type of intervention**
Treatment.

**Economic study type**
Cost-effectiveness analysis and cost-utility analysis.

**Study population**
The study population comprised a cohort of lymph node-positive premenopausal women.

**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 1976 and 2000. The resource use and cost data were, in part, obtained from sources published from 1991 to 2001. The price year was 2000.

**Source of effectiveness data**
The effectiveness evidence was derived from a synthesis of completed studies and authors' assumptions.

**Modelling**
A Markov model was constructed to determine the costs and benefits of mastectomy and chemotherapy alone versus mastectomy, chemotherapy and PMRT in a hypothetical cohort of node-positive 45-year-old women. The health states used in the model described the conditions of being well, having isolated local-regional failure (LRF), having recurrent local-regional and/or distant disease, and undergoing successful salvage therapy after (LRF). These were in addition to death from breast cancer and death from other causes. The time horizon was 15 years (although some outcomes were estimated at 10 years) and the cycle length was 6 months. A structure of the model was reported. A second model, based on a decision tree, was also used to describe the outcomes of breast cancer relapse with and without PMRT.

**Outcomes assessed in the review**
The outcomes estimated from the literature were:

the risk of relapse with and without PMRT;
salvage of LRF;
the progression of recurrent disease with and without PMRT;
death due to breast cancer;
other-cause mortality; and
the utility values associated with specific health states.

Study designs and other criteria for inclusion in the review
It was not stated whether a systematic review of the literature had been undertaken to identify primary studies. Some evidence came from clinical trials and meta-analyses, while other model inputs were estimated from cohort studies or national statistics. No other details on the sources of the data were provided.

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 26 primary studies provided evidence.

Methods of combining primary studies
The primary studies appear to have been combined using a narrative method.

Investigation of differences between primary studies
Not reported.

Results of the review
Only some clinical estimates will be reported in this abstract.

The annual hazard of breast cancer recurrence declined from 0.143 in the first year to 0.005 after 15 years without PMRT, and from 0.118 in the first year to 0.003 after 15 years with PMRT.

The probability of moving from disease relapse to isolated LRF was 0.30 without PMRT and 0.10 with PMRT.

The probability of moving from disease relapse to distant disease was 0.54 without PMRT and 0.82 with PMRT.

The probability of moving from disease relapse to combined disease was 0.16 without PMRT and 0.08 with PMRT.

The probability of moving from isolated LRF to salvaged (successfully treated) and local-regional disease (unsuccessfully treated or not treatable) were 0.80 and 0.10, respectively, without PMRT and 0.30 and 0.70 with PMRT.
For women aged 45 to 60 years, the annual mortality rate was less than 1% (range: 0.22 - 0.85).

The utility weights were 0.72 with adjuvant chemotherapy, 0.68 with PMRT, 0.85 in the well health state, 0.82 in the salvaged state, 0.54 with local-regional disease and combined disease, and 0.62 with distant disease.

**Methods used to derive estimates of effectiveness**
The authors made some assumptions that were used in the decision model.

**Estimates of effectiveness and key assumptions**
The pattern of failure was assumed to have been constant over time.

After disease recurred distantly, no patient could be successfully treated with salvage therapy or return to the well state.

The rate of disease progression after PMRT was similar to that without PMRT.

The utility values for the well health state were similar after either chemotherapy or chemotherapy and PMRT.

**Measure of benefits used in the economic analysis**
The summary benefit measures used were the life-years (LYs) estimated at 15 years, quality-adjusted life-years (QALYs) at 15 years, and LRF at 10 years. All measures were derived using the modelling approach and were discounted at an annual rate of 3%. The utility values were obtained from published sources and were estimated using time trade-off, standard gamble and a visual analogue scale.

**Direct costs**
Discounting was relevant because of the long timeframe of the study and an annual rate of 3% was used. The costs were presented as macro-categories. The unit costs were not reported separately from the quantities of resources used. The health services included in the economic evaluation were PMRT (including professional and technical services, and transportation), adjuvant chemotherapy, salvage therapy for initial local failure, death from breast cancer, follow-up in the well health state, advanced recurrent disease, and terminal breast cancer. The cost/resource boundary of the study was that of society. The resource use data were derived from published sources and authors’ assumptions. The costs were derived from average reimbursement by private insurers at the University of Michigan, typical transportation costs, published studies and Medicare payments. The price year was 2000.

**Statistical analysis of costs**
The costs were treated deterministically in the base-case.

**Indirect Costs**
Indirect costs were considered in the economic evaluation because a societal perspective was adopted. In particular, productivity losses from time spent travelling to and undergoing consultation, simulation and treatment for PMRT were considered. The unit costs and the quantities of resources used were reported separately. Resource use was mainly based on authors’ assumptions, while the unit cost was derived from the average hourly wage for women in their 40s.

**Currency**
US dollars ($).

**Sensitivity analysis**
Several sensitivity analyses were carried out to examine the robustness of the cost-effectiveness of PMRT to variations.
in the model inputs. Univariate sensitivity analyses were performed on several variables. In particular, the age of the cohort, the cost of PMRT, the cost of recurrent disease, the 10-year risk of recurrent disease, the local-regional salvage rate after chemotherapy, the discount rate, and the utility values for well state and for well state after radiation therapy, were varied. A two-way sensitivity analysis was performed on the cost of radiation and 10-year risk of relapse. A Monte Carlo simulation was used to determine the confidence interval for the cost-effectiveness ratio and the probability that the cost per QALY was below the threshold of $50,000. Most of the ranges used in the sensitivity analysis were derived from the literature, while some estimates were based on authors’ assumptions.

**Estimated benefits used in the economic analysis**

The estimated discounted LYS (15 years) were 8.75 with no PMRT and 9.04 with PMRT (difference 0.29). The estimated discounted QALYs (15 years) were 7.03 with no PMRT and 7.35 with PMRT (difference 0.32).

The estimated LRF (at 10 years) was 24% with no PMRT and 8% with PMRT (difference 16%; odds ratio 0.24).

Overall survival was 59% at 10 years and 49% at 15 years with no PMRT versus 63% (10 years) and 55% (15 years), respectively, with PMRT.

**Cost results**

The first-year costs were $10,500 with no PMRT and $22,000 with PMRT (difference $11,500).

The costs of recurrence were $22,800 with no PMRT and $18,000 with PMRT (difference $4,800).

The 15-year costs were $40,800 with no PMRT and $48,100 with PMRT (difference $7,300).

**Synthesis of costs and benefits**

Incremental cost-effectiveness and cost-utility ratios were calculated to combine the costs and benefits of the alternative strategies.

The incremental cost per LY gained with PMRT over no PMRT was $24,900.

The incremental cost per QALY gained with PMRT over no PMRT was $22,600.

The incremental cost per LRF avoided with PMRT over no PMRT was $43,400.

The sensitivity analysis showed that, in general, the cost per LY saved remained below the value of $33,000 under most scenarios. However, the base-case results were sensitive to the cost of PMRT and the risk of cancer recurrence.

The cost-effectiveness ratio varied between $5,300 and $64,200 with a 50% reduction and 100% increase in the cost of radiation therapy. Similarly, the cost-effectiveness ratio fell to $11,500 with an 80% 10-year breast cancer recurrence rate (LRF 37%) and increased to $90,400 with a 20% 10-year recurrence rate (LRF 9%).

The two-way sensitivity analysis showed that the cost per LY saved remained below the threshold of $50,000 over a wide range of possible values.

The Monte Carlo simulation generated a mean cost-utility ratio of $28,500 (95% confidence interval: 7,100 - 72,000), and 90% of simulations fell below the threshold of $50,000 per QALY.

**Authors’ conclusions**

Postmastectomy radiation therapy (PMRT) was cost-effective for node-positive premenopausal patients in comparison with mastectomy and chemotherapy alone. The cost-effectiveness of PMRT was $22,600 per life-year (LY) saved, which compared favourably with other widely adopted medical and cancer therapies.
CRD COMMENTARY - Selection of comparators
The selection of the comparator (mastectomy and chemotherapy alone) reflected the standard pattern of care for node-positive premenopausal women. You should decide whether this is a valid comparator in your own setting.

Validity of estimate of measure of effectiveness
The effectiveness evidence came from several published studies. It was not stated whether a systematic review of the literature had been undertaken. In effect, the primary studies appear to have been identified selectively. Limited information on the design of the primary studies was reported. Some evidence came from clinical trials and meta-analyses, which enforces the internal validity of the analysis. However, details on the sample size and patient characteristics were not given. The methods used to extract and combine the data were not described clearly. Key model inputs were varied in the sensitivity analysis.

Validity of estimate of measure of benefit
Several benefit measures were used. The use of QALYs as a summary benefit measure was appropriate as it incorporated the impact of the interventions on survival and quality of life. The methods used to obtain utility values were provided, although details were sparse. Discounting was applied, as recommended in US guidelines. QALYs and LYS are comparable with the benefits of other health care interventions.

Validity of estimate of costs
The cost categories included in the economic evaluation were consistent with the perspective stated. Limited information on the unit costs and quantities of resources used for the direct costs was provided, as many of the costs were presented as macro-categories. This limits the possibility of replicating the analysis in other settings. Economic inputs came from multiple sources, including authors' assumptions for some resource use data. The costs were specific to the study setting but some estimates were varied in the sensitivity analysis. The price year was reported, which enables reflation exercises to be conducted.

Other issues
The authors compared their findings with those from other published studies that showed different values of the cost-effectiveness of PMRT. The issue of the generalisability of the study results to other settings was not explicitly addressed, although the use of extensive sensitivity analyses enhanced, in part, the external validity of the analysis. The authors stated that the actuarial curves representing LRF and survival were consistent with those reported in actual randomised trials, which validated the results of the decision model. It was noted that the potential long-term morbidity resulting from PMRT was not considered in the model. The authors pointed out that some data were derived from non-US trials given the lack of US-trials, thus the transferability of the results is subject to caution. A further limitation of the analysis was the simplification required in the decision model.

Implications of the study
The study results supported the use of PMRT in premenopausal women who are node-positive. The authors suggested that survival projections into a longer time horizon might further improve the cost-effectiveness of PMRT. It was stressed that the issue of quality of life associated with PMRT requires further investigation. The authors noted that the cost-effectiveness of PMRT in sub-groups of patients, such as those with four or more involved nodes and/or large tumours, and those with one to three nodes, is currently under investigation.

Source of funding
None stated.

Bibliographic details
Lee J H, Glick L A, Hayman J A, Solin L J. Decision-analytic model and cost-effectiveness evaluation of

PubMedID
12039934

Other publications of related interest


Indexing Status
Subject indexing assigned by NLM

MeSH
Aftercare /economics; Breast Neoplasms /economics /mortality /pathology /radiotherapy /surgery; Cost-Benefit Analysis; Decision Support Techniques; Disease-Free Survival; Female; Humans; Lymphatic Metastasis; Markov Chains; Mastectomy; Middle Aged; Models, Econometric; Premenopause; Quality-Adjusted Life Years; Radiotherapy, Adjuvant /economics; Reproducibility of Results; Sensitivity and Specificity; Survival Rate; Value of Life

AccessionNumber
22002001027

Date bibliographic record published
30/09/2005

Date abstract record published
30/09/2005