Cost-effectiveness of new guidelines for adjuvant systemic therapy for patients with primary breast cancer


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 guidelines for the use of adjuvant systemic therapy for patients with primary breast cancer (BC). Adjuvant systemic therapy could consist of chemotherapy and/or endocrine therapy. Endocrine therapy comprised tamoxifen for 5 years (20 mg/day). Polychemotherapy comprised the classic CMF regimen (cyclophosphamide, methotrexate, 5-fluorouracil) for 6 cycles. Combination therapy consisted of the CMF regimen followed by a 5-year period of tamoxifen. Three guidelines adopted in the Netherlands were considered.

The first strategy was conventional therapy (CT), which consisted of adjuvant therapy for node-positive (N+) patients and no therapy for node-negative (N0) patients.

The second strategy was the guideline introduced in 1998, which changed CT for patients with N0 disease. These patients were categorised into low and high risk (high risk was defined by primary tumour characteristics such as tumour size and grade of differentiation or mitotic activity index). High-risk patients received adjuvant systemic therapy.

The third strategy was the 2001 modification of the 1998 guideline. This modified guideline recommended that patients aged 35 years or younger were always to be treated with adjuvant systemic therapy, regardless of the lymph node status or primary tumour characteristics. In addition, postmenopausal women aged 50 to 59 years with a hormone receptor-positive tumour were recommended for adjuvant chemotherapy, in addition to adjuvant endocrine therapy.

Type of intervention
Treatment and palliative care.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised a hypothetical cohort of patients with primary BC.

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

Dates to which data relate
The effectiveness data were derived from a sample of patients in 1999 and from studies published between 1992 and 1998. No dates for resource use were reported. The price year was not given.

Source of effectiveness data
NHS Economic Evaluation Database (NHS EED)
Produced by the Centre for Reviews and Dissemination
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The effectiveness evidence was derived from a synthesis of published studies, a series of patients (single study), and expert opinion.

**Link between effectiveness and cost data**
The costing was carried out on a sample of patients that was different from that considered in the primary study.

**Study sample**
A sample of 127 consecutive patients with primary BC operated on in 1994 was considered. The mean age of these patients was 58 years (1.6% aged 35 years or younger, 29.9% aged 36 - 49, 22.8% aged 50 - 59 years, 24.4% aged 60 - 69, and 21.3% aged 70 or older). In terms of nodal status, 59.8% were N0 and 40.2% were N+. Only patients with histologically proven invasive BC, in whom a modified radical mastectomy or BC surgery with an axillary lymph node dissection (ALND) was performed, were included. Patients who had an ipsilateral BC in the past (prior ALND) or who were classified as having M1 or T4 disease (TNM classification) were excluded. Power calculations suggested that a sample of 110 patients would have been required to assess the percentage of patients eligible for adjuvant therapy with 8% accuracy and a 95% confidence interval (CI).

**Study design**
This was a historical case series study. Patients were retrospectively identified from three participating studies (one university hospital and two regional teaching hospitals). No follow-up was performed.

**Analysis of effectiveness**
The main outcome measure was the percentage of patients eligible for adjuvant systemic therapy according to the three guidelines. Other probability data that were used as model inputs were epidemiological data such as the nodal status of the patients, tumour size and postmenopausal condition. All of these inputs were reported in the technical appendix.

**Effectiveness results**
The proportion of BC patients eligible for adjuvant therapy would be 40.2% with CT, 71.7% with the 1998 guidelines, and 71.7% with the 2001 guidelines.

Among the numerous probability values:

- the probability that a BC patient is N+ was 0.398;
- the probability that a BC patient is N+ and hormone receptor-positive (ER+ or PgR+) was 0.659;
- the probability that a BC patient is N+ and ER+ or PgR+ and postmenopausal was 0.586;
- the probability that a BC patient is N+ and ER+ or PgR+ and postmenopausal and aged at least 70 years was 0.412; and
- the probability that a BC patient is N+ and ER- and PgR- and postmenopausal was 0.667.

Other probabilities used to populate the decision tree were also reported.

**Clinical conclusions**
The clinical inputs derived from the sample of women with BC were used as model inputs in the decision model.

**Modelling**
A decision model was constructed to assess the costs and benefits associated with the three guidelines for the treatment of women with BC. The structure of the model, which was reported, reflected the three strategies. Thus, patients in the
CT arm received adjuvant therapy only if they were N+. Patients in the 1998 guideline arm received adjuvant therapy if N+ and, under certain circumstances, if N0. N0 patients received adjuvant therapy if the tumour size was larger than 3 cm, or if it was between 1 and 3 cm but they had additional risk factors (mitotic activity index >= 10 or Bloom-Richardson differentiation grade III). Patients in the 2001 guideline arm followed the same pathway of patients in the 1998 guideline arm, with the exception that individuals younger than 35 years received adjuvant therapy regardless of the lymph node status or primary tumour characteristics. The model was populated with data derived from multiple sources, such as a series of patients treated in teaching hospitals in the Netherlands, published evidence and expert opinion. The time horizon was 10 years.

Outcomes assessed in the review
The outcome estimated from the literature was the 10-year overall survival rate for different sub-groups of patients defined according to nodal status, postmenopausal condition and age.

Study designs and other criteria for inclusion in the review
The clinical data were derived from the Early Breast Cancer Trialists’ Collaborative Group (EBCTCG) meta-analysis.

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
Four primary studies provided the clinical data.

Methods of combining primary studies
A meta-analysis was used to combine the primary estimates.

Investigation of differences between primary studies
Not reported.

Results of the review
The 10-year overall survival rate was:

30% for N+, ER+ or PgR+, postmenopausal, >70 years, with tamoxifen;
62% for N+, ER+ or PgR+, postmenopausal, <70 years, with tamoxifen;
62% for N+, ER+ or PgR+, postmenopausal, 60 - 69 years, with tamoxifen;
15% for N+, ER-, PgR-, >70 years, no therapy;
49% for N+, ER-, PgR-, postmenopausal, polychemotherapy;
53% for N+, ER-, PgR-, premenopausal, polychemotherapy; 
90% for N0, low risk, no therapy; 
65% for N0, high risk, ER+ or PgR+, postmenopausal, \( \geq 70 \) years, with tamoxifen; 
69% for N0, ER-, PgR-, postmenopausal, polychemotherapy; and 
78% for N0, ER-, PgR-, premenopausal, polychemotherapy.

**Methods used to derive estimates of effectiveness**
Two experts estimated 10-year overall survival if data were not available from published studies.

**Estimates of effectiveness and key assumptions**
The 10-year overall survival rate was:

- 64% for N+, ER+ or PgR+, postmenopausal, 50 - 59 years, with combination therapy;
- 70% for N+, ER+ or PgR+, premenopausal, with combination therapy;
- 80% for N0, no therapy;
- 86% for N0, high risk, ER+ or PgR+, premenopausal or <35 years, combination therapy; and
- 78% for N0, less than 35 years, ER- or and PgR-, polychemotherapy.

**Measure of benefits used in the economic analysis**
The summary benefit measure was the expected number of life-years (LYs) gained. This was derived using a decision modelling approach. The 10-year overall survival was also reported as a model output. A 4% annual discount rate was applied to assess the present value of future benefits.

**Direct costs**
The cost analysis took the perspective of the health care system. It included the direct medical costs of drugs, personnel, blood tests, equipment use, annual mammography, anti-emetics and overheads. Although the unit costs were reported, the quantities of resources used were not explicitly given. The source of the resource use data was unclear. The costs were estimated from some teaching hospitals and other typical sources for the Netherlands. Discounting was relevant, as 10-year costs were estimated, and an annual rate of 4% was used. The price year was not reported.

**Statistical analysis of costs**
The costs were treated deterministically.

**Indirect Costs**
The indirect costs were not included.

**Currency**
Euros (EUR).

**Sensitivity analysis**
Univariate sensitivity analyses were carried out to assess the robustness of the cost-effectiveness ratios to variations in a number of model inputs, such as the discount rate (0% or 6% for both costs and benefits) and the probability of having a primary tumour with a specific diameter. Alternative ranges of values for the probability values were derived from the sample of patients. A probabilistic sensitivity analysis was also performed, using a Monte Carlo simulation to generate CIs for overall survival.

**Estimated benefits used in the economic analysis**

The expected LYs (10-year overall survival) in all patients were 7.37 (47.3%) with CT, 7.44 (48.7%) with the 1998 guidelines and 7.42 (48.4%) with the 2001 guidelines.

The corresponding values in the sub-group of N0 patients were 7.68 (53.5%) with CT, 7.80 (55.9%) with the 1998 guidelines and 7.79 (55.9%) with the 2001 guidelines.

**Cost results**

The expected 10-year costs were EUR 1,773.40 with CT, EUR 2,133.82 with the 1998 guidelines and EUR 2,153.03 with the 2001 guidelines.

The corresponding values in the sub-group of N0 patients were EUR 1,277.59 with CT, EUR 1,876.31 with the 1998 guidelines and EUR 1,876.68 with the 2001 guidelines.

**Synthesis of costs and benefits**

Incremental cost-effectiveness ratios (ICERs; i.e. the incremental cost per LY saved) were calculated to combine the costs and benefits of the alternative guidelines. The ICER of 1998 over CT was EUR 4,873, while 2001 guidelines were dominated by 1998 guidelines, which were both more effective and less expensive. The same results were observed in the sub-group of N0 patients.

The univariate sensitivity analysis showed that if survival rates were not discounted, then the ICER would be EUR 3,268. Variations in other data did not alter substantially the results of the base-case analysis.

The probabilistic sensitivity analysis showed that the mean ICER would have been EUR 4,240 (95% CI: 3,604 to 4,505) for the 1998 guidelines over CT.

**Authors' conclusions**

The introduction of new guidelines for the management of women with breast cancer (BC) in the Netherlands in 1998 led to a substantial increase in the number of patients eligible for adjuvant systemic therapy, but the incremental cost-effectiveness ratio (ICER) relative to the previous guideline was well within the range of values that are generally considered acceptable. Treatment according to 2001 guidelines was slightly more expensive but no more effective. Thus, the optimal guideline was that implemented in 1998.

**CRD COMMENTARY - Selection of comparators**

The rationale for the choice of the comparators was clear since the new guideline (and its update) was compared with the standard approach in the Netherlands. A clear description of the different guidelines was provided. You should decide whether they are valid comparators in your own setting.

**Validity of estimate of measure of effectiveness**

The effectiveness evidence came from different sources. Some data were estimated from a sample of patients admitted to three teaching hospitals in the Netherlands. Some statistical analyses were carried out to determine the most appropriate number of patients required to have sufficient power for the analysis. A second source of data was a published meta-analysis (presumably of clinical trials), which would usually have a high internal validity. However, no
details of the meta-analysis were reported. Finally, given the lack of published evidence for all types of patients, the opinions of some of the authors were used. Only one of the clinical inputs was varied in the sensitivity analysis. A more extensive use of sensitivity analyses for all uncertain clinical data would have been more appropriate, given the use of mixed sources.

Validity of estimate of measure of benefit
The summary benefit measure (LYs) was appropriate since it captured the impact of the different guidelines on the most important dimension of health for BC patients. The assessment of other aspects such as quality of life would have been interesting, but the authors stated that such data do not exist. Discounting was carried out, and the impact of using an alternative discount rate or not discounting was investigated in the sensitivity analysis.

Validity of estimate of costs
The categories of costs included in the analysis were appropriate for the perspective adopted in the study. A detailed breakdown of the cost items and their unit costs was reported, but little information on resource consumption was provided. This might limit the possibility of replicating the analysis in other countries. Further, no statistical analyses of the costs were carried out, and the cost estimates were specific to the study setting since no sensitivity analyses were performed. The price year was not reported, which makes reflation exercises in other time periods difficult. The sources of the costs reflected the Dutch health care system.

Other issues
The authors noted that no economic evaluations of guidelines for adjuvant systemic therapy have been published, thus comparisons with other studies were not possible. The issue of the generalisability of the study results to other settings was not addressed. In addition, the external validity of the analysis was likely to be low, given that few sensitivity analyses were carried out. The authors noticed that 100% compliance with the guidelines was assumed, which seems unrealistic. However, this assumption should not have biased the results in favour of a specific guideline. Instead, the main limitation of the study appears to have been the poor analysis of the uncertainty around key model parameters. The study referred to the treatment of women with BC and this was reflected in the authors’ conclusions.

Implications of the study
The study results supported the implementation of 1998 guidelines for adjuvant systemic therapy for patients with primary BC.

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None stated.

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