COST-EFFECTIVENESS OF USING DIFFERENT PROGNOSTIC INFORMATION AND DECISION CRITERIA TO SELECT WOMEN WITH EARLY BREAST CANCER FOR ADJUVANT SYSTEMIC THERAPY.*

WORK IN PROGRESS. PLEASE DO NOT QUOTE WITHOUT PERMISSION.

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Abstract

Background: In the UK prognostic information is routinely used to select women with early breast cancer for adjuvant systemic therapy. This paper reports on the cost-effectiveness of using a range of different prognostic indices and decision criteria.

Methods: Costs and QALYs with and without adjuvant chemotherapy were modelled using a patient level dataset containing survival data and prognostic information for women treated at the Clinical Oncology Unit at the Churchill Hospital, Oxford. Life expectancy beyond the available minimum 5-year follow-up data was estimated using an exponential function and life tables; costs, utilities, treatment effects and side effect probabilities were obtained from the published literature. The current protocol, the Nottingham Prognostic Index, an Oxford Prognostic Index (estimated directly from the patient level dataset), net quality adjusted life expectancy and expected cost per QALY were each then used to predict which women would be selected for adjuvant chemotherapy, and the population incremental cost per QALY of each decision criteria was calculated in comparison with the current protocol.

Results: Treatment decisions based on a single prognostic index value are not cost-effective compared to current protocol. Treating all women, or treating based on anticipated gain in quality-adjusted life expectancy produced incremental cost per QALY values above £30,000 per QALY. Selecting women for adjuvant chemotherapy on the basis of expected individual cost-effectiveness was the most economically efficient strategy.

Conclusions: Decisions about how to use prognostic information or other criteria to guide treatment decisions for women with early breast cancer appear to be associated with quite different levels of cost-effectiveness. The use of expected individual cost-effectiveness ratios to guide treatment decisions and protocols is a promising approach and worthy of further examination in this and other treatment areas.

Introduction

Although cost-effectiveness analysis is fundamentally concerned with making choices about which patients or groups of patients should be offered which interventions, little explicit attention has been paid by health economists to the use of prognostic indices in making treatment choices, although these potentially provide a reasonable quantitative prediction of health outcome and therefore are likely to be associated with cost-effectiveness. A structured review of published cost-effectiveness studies of prognostic markers identified only 5 such studies in any therapeutic or disease area (Calvert et al., Littrup et al., Mason et al., Glance et al., Hamel et al). Three papers reported on the cost-effectiveness of using prognostic information in cancer detection or treatment (Calvert et al., Littrup et al., Mason et al.). Intensive care provided the setting for the remaining two studies (Glance et al., Hamel et al.).

Prognostic indices raise at least two issues from an economic perspective: first, what are the incremental costs and effects of making treatment choices for patients or groups of patients on the basis of a prognostic index, compared to some other decision rule such as treating all patients; second, given that individual prognostic factors or composite prognostic indices have varying accuracy and that resources may be involved in using them, can a cost-effectiveness framework provide a method of determining how much is worth spending in acquiring prognostic information?

In this paper we set out a generic method for estimating the cost-effectiveness of using prognostic information to inform patient treatment decisions. Firstly, the treatment area used to demonstrate the methodology is introduced. Early breast cancer provides the setting and the treatment decision of whether or not to offer women adjuvant chemotherapy. We then present four sections detailing the different steps in our analysis. In the first section, a patient-specific dataset upon which all subsequent analyses are performed is introduced. The second section describes the methods used to develop a new prognostic index – referred to here as the Oxford Prognostic Index (OPI). The third section describes the economic model used in the estimation of the lifetime costs and outcomes (life expectancy and quality adjusted life expectancy) for each patient in the dataset, in the presence or absence of adjuvant chemotherapy, and finally the fourth section presents the results of an analysis estimating the incremental cost per life year gained and per quality adjusted life year gained of using a number of prognosis-based decision rules to guide adjuvant therapy treatment decisions for each individual in the dataset. Although this analysis focuses on adjuvant chemotherapy for early breast cancer, the general approach should be applicable to other types of prognostic information, interventions and disease areas.

Treatment Area: Adjuvant chemotherapy for early breast cancer.

Breast cancer is the most common cancer occurring in women worldwide and is the leading cancer-related cause of death for women in Europe (DoH 2002, Bray 2002). For women defined as having ‘early’ breast cancer, detectable disease is confined to the breast and / or the axilla and can be removed by surgical resection. The possibility exists however that undetectable micro-metastatic disease may have been deposited elsewhere in the body, causing eventual systemic relapse and death. The aim of adjuvant systemic therapy (of which two types exist) is to eradicate this residual disease. Tamoxifen, the most widely used adjuvant hormone therapy works by interfering with the production of oestrogen, which promotes the growth of breast cancer cells. Adjuvant chemotherapy involves administering a combination of anti-

cancer (cytotoxic) drugs which work to destroy cancer cells directly. Both types of therapy may be given alone or in combination.

Breast cancer is acknowledged as being a clinically heterogeneous disease and therefore some uncertainty exists about which patients may and may not benefit from adjuvant therapy. Some women suffer a relapse despite receiving therapy, whilst others survive without recurrence even in the absence of such treatment. In recent decades studies have investigated the importance of many clinical factors in predicting relapse and death from breast cancer and several prognostic indices have been developed. Amongst the factors widely accepted as having prognostic value are lymph node involvement, and histological grade and size of the primary tumour. These three factors were combined to create the Nottingham Prognostic Index (NPI) for primary breast cancer, which although developed in the early 1980s, was revealed in a recent survey of lead clinicians at UK breast cancer units to be still the most commonly used prognostic index for aiding with selection of women for adjuvant systemic therapy (Haybittle et al. Todd et al.). A patient's index score is calculated using the linear predictor from a cox proportional hazards model and involves summing tumour grade (scored 1, 2, or 3) with tumour stage (scored 1 = no nodal involvement, 2 = 1-3 nodes positive, and 3 = 4 or more nodes positive) and 0.2 x tumour size in centimetres (Todd et al.). NPI index values commonly used to discriminate between patients with differing prognoses are: less than 3.4 = good prognosis, 3.4 to 5.4 = moderate prognosis, 5.4 upwards = poor prognosis.

Factors likely to predict a patient's response to therapy have also been explored. It is for example now widely accepted that any woman having a tumour positive for hormone receptors (oestrogen (ER) and/or progesterone (PR) receptors) should receive Tamoxifen. A greater response to the drug has been demonstrated for these women than for women with ER or PR negative tumours for whom the benefit has been shown to be much smaller (EBCTG).

Much less consensus exists about how to select women for treatment with adjuvant chemotherapy. A variety of prognostic index or marker-based guidelines are currently routinely used for this purpose in the UK with the aim of enabling a more precise targeting of chemotherapy towards individuals in whom its use is likely to be effective. With this inconsistency in mind we set about estimating a new prognostic index, and developed a methodology to enable the cost-effectiveness implications of using it and other prognostic information based decision algorithms to select adjuvant chemotherapy for individual or groups of women following surgery for early breast cancer.

The patient dataset

A patient-level data set was obtained from the Medical Oncology Unit at the Churchill Hospital, Oxford. The dataset contained information on personal and clinical characteristics, treatments and outcomes (relapse and death) for some 1,174 women with operable breast cancer treated at the unit from 1987 onwards. Minimum length of follow-up was five years.

Although 1,174 patients were potentially available for the analysis, items of information were missing for some patients. Table 1 details the degree of missingness and shows quite clearly that the proportion of missing values was low in almost all

variables except ER levels, which were not available for 342 (29.1%) of the 1,174 cases.

Given the potential prognostic importance of this variable (patients whose cancers have ER positive receptors tend to have a better prognosis than patients whose cancers do not have these receptors) and given that cancers with ER positive receptors are also more likely to respond to chemotherapy or hormone treatment, it was decided to impute a value for ER level where it was missing, but to drop all other cases where at least one variable had a missing value. Details of the imputation process used are available from the authors upon request, as is complete descriptive information on the final dataset, which comprised of 1,058 observations. Table 2 summarises patient characteristics.

Methods

An updated survival model: the Oxford Prognostic Index

Survival analysis was employed using the patient characteristics presented in table 1 as potential prognostic factors for time to breast cancer death in this patient group. Although non-parametric methods are commonly employed in medical statistics, we chose to parameterise the survival function since the survival analysis would form the basis of the economic model (see below) which requires the baseline hazard function to be known. Three potential parametric models for survival time were considered, exponential, Weibull and Gompertz, which are capable of modelling constant, monotonically increasing or monotonically decreasing hazard functions. We chose not to consider other common functional forms, such as lognormal or log logistic, since the lack of montonicity can sometimes lead to unrealistic hazard functions when extrapolated. Both Weibull and Gompertz models nest the exponential distribution as a special case but tests revealed that within the data there was no evidence for moving away from a simple exponential model of constant hazard. The final model that we selected is reproduced in Table 3.

Note from table 3, that dummy variables for treatment with chemotherapy and hormone treatment were included. The purpose of this is not to estimate treatment effects, since it is well known that observational data such as these suffer selection biases in this regard. Rather the purpose was to adjust for treatment in order to generate a predicted survival in the absence of treatment (achieved by setting the treatment dummy variables to zero).

In order to generate the OPI, we first calculated the linear predictor (the cross product of the coefficients in Table 3 with the prognostic factors) for each patient in the dataset, and setting the treatment dummy variables to zero. This generated a variable that ranged from –11.5 to –6.4 to which 12 was added in order to generate a prognostic index on the range 0.5 to 5.6, where 0.5 represents a good and 5.6 a poor prognosis. It should be clear from the description above that the OPI has a direct relationship with the linear predictor in an exponential survival analysis. Nevertheless, it is instructive to consider grouping the OPI into prognostic groups and presenting the survival curves for such groups. To determine the index scores that best discriminate on the basis of prognosis, various ways of classifying women into prognostic groups were examined. Issues considered when constructing groups were loss of information about differences between individuals (Cox D.R 1957), degree of

separation between Kaplan Meier survival curves, and the number of groups considered practical for use in a clinical setting.

A model for the cost and (quality adjusted) survival of breast cancer patients
The exponential survival model estimated directly from the patient dataset was also used to extrapolate the probability of breast cancer death over the 15 years following diagnosis, and this formed the basis of a cost-effectiveness model. Account was also taken of non-breast cancer deaths during this time period, rates for which were obtained from the Government Actuary's Department. Survival for women beyond 15 years was modelled using age adjusted population norms taken from published life table data (Government Actuary's Department). Since the effect of breast cancer on survival attenuates over time, to capture this and avoid discontinuity on the survival curve at the point where the combined exponential / non breast cancer death model gives way to life table data, the predicted breast cancer death hazard was reduced between years 11 and 15 from 1 (full effect) to 0 (no effect) in increments of 0.2. Within the cost-effectiveness model, it was assumed that each death from breast cancer was preceded by a breast cancer recurrence with associated quality of life decrements and costs. For simplicity, non-fatal breast cancer recurrences were not separately modelled.

To ensure that treatment effects could be examined within the model, indicator variables for adjuvant chemotherapy and adjuvant hormone therapy were included when estimating the exponential survival model, and these were set to zero when the linear predictor (OPI) was calculated. It was decided that more robust estimates of the treatment effects of adjuvant chemotherapy and adjuvant hormone treatment would be obtained from the Early Breast Cancer Trialists' Group (EBCTG) overviews than from the patient database, so rather than adjust the model's hazard prediction using the coefficients attached to the treatment indicator variables, relative risk values taken from the published EBCTG overviews were obtained. Table 4 reports the values used in the model: in summary, it is assumed that hormone treatment has no effect on ER negative women, and has a relative risk of 0.76 for women who are ER positive. For chemotherapy, the relative risk reduction is related to age, with a relative risk of 0.78 for those aged less than 50, 0.89 for those aged 50-59 and 0.92 for those over 60.

The probabilities of experiencing side effects of treatment, and of consequent costs and utility decrements, were obtained from previously published studies, as were costs and utility decrements associated with relapse. Health service costs associated with the following were also included: adjuvant chemotherapy (*such as CMF); adjuvant hormone therapy (tamoxifen); and recurrence. All costs and outcomes were discounted at an annual rate of 3% (UK Treasury). Table 5 summarises the parameter values used in the cost-effectiveness model, with details of the source of information. All costs are expressed in 2002 prices.

Running the model described above, enabled an estimation of the lifetime costs and outcomes (life expectancy and quality adjusted life expectancy) for each patient in the dataset, in the presence or absence of adjuvant chemotherapy treatment or hormone treatment. For simplicity, the main analyses focused on the chemotherapy decision. It was assumed that all ER positive patients and no ER negative patients received hormone treatment.

Modelling patient selection using different prognostic criteria: costs and outcomes

A series of different decision criteria were each examined in turn, and used to identify those patients in the dataset who would have been selected to receive or not receive adjuvant chemotherapy:

- the current (2002) treatment protocol of the Medical Oncology Unit at the Churchill Hospital, Oxford
- cut-off values using the Nottingham Prognostic Index
- cut-off values using the Oxford Prognostic Index
- a net health gain rule, whereby treatment is offered to a patient if the model predicts a gain in quality adjusted life expectancy (that is, survival benefit outweighs disutilities from side-effects and/or recurrrence
- a cost-utility rule, whereby treatment is offered to a patient if the model predicts that the cost per quality adjusted life year gained of treatment over no treatment is less than £30,000.
- actual treatment choice
- treat all patients
- treat no patients.

Once patients had been allocated to treatment or no treatment under each decision rule, total costs and effects were summed across all patients and the results of each strategy were plotted on a cost-effectiveness plane. The current protocol was taken as the comparator to calculate incremental cost-effectiveness results. Sensitivity, specificity and positive and negative predictive values for each strategy were also calculated, taking the cost-effectiveness approach as the "gold standard".

Sensitivity analysis

Using this model structure, it was possible to explore the effect of altering the threshold/cut-off points used to determine treatment when basing decisions on the NPI or OPI; the effect of changes in the cost per QALY ceiling ratio was also examined.

Results

The Oxford Prognostic Index (OPI)

Figure 1 shows the distribution of OPI scores for the 1058 patients in the dataset. The scores were fairly normally distributed with a mean index value of 2.24 (SD 0.88). Four prognostic groups (constructed by splitting the ascending OPI scores using normal distribution percentages) appeared to give a good discrimination on the basis of prognosis, and were considered a practical number of groups for use in a clinical setting. Figure 2 shows the survival curves plotted for each group. The corresponding OPI cut-off values were <1.37, 1.37 to <2.15, 2.15 to <3.05 and ≥ 3.05.

Illustrative predictions from the cost-effectiveness model

Figures 3a and 3b show the way in which the model predicts survival following breast cancer surgery for two hypothetical women: a) a 45 year-old woman with a tumour of size 1cm, stage 1 and grade 1, who is ER positive, and b) a 65 year old woman with a tumour of size 3cm, stage 3 and grade 2, who is ER negative.

In Figure 3a, the woman's characteristics indicate excellent prognosis, and this is evident in the figure: the 10 year probability of survival is 0.94 if adjuvant chemotherapy is not given and 0.95 if it is given, and quality adjusted life expectancy (undiscounted) is 26.56 years if no adjuvant chemotherapy is given and 26.69 if adjuvant chemotherapy is given; the (discounted) cost-effectiveness of treatment compared to no treatment is £52,500 per QALY gained. In Figure 3b the woman's characteristics indicate poor prognosis: the 10 year survival probability is 0.27 if adjuvant chemotherapy is not given and 0.30 if it is given; quality adjusted life expectancy (undiscounted) is 5.58 years if no adjuvant chemotherapy is given and 5.84 if adjuvant chemotherapy is given, and the (discounted) cost-effectiveness of treatment compared to no treatment is £11,400 per QALY gained.

Patient selection using different prognostic criteria: costs and outcomes

Table 6 shows descriptive results of applying different prognostic criteria when deciding which women to select for adjuvant chemotherapy. In practice, 26% of women in the sample were given adjuvant chemotherapy, and the estimated discounted quality adjusted life expectancy of all patients based on this selection criterion was 11.03 years. If the current protocol had been applied to all patients in the database, 35% would have been given adjuvant chemotherapy with a slight increase in overall quality adjusted life expectancy. Using a cost-effectiveness ceiling of £30,000 per QALY gained to select patients, 569 would have been given adjuvant chemotherapy, while treating if there was any anticipated net gain in quality adjusted life expectancy would result in 90% of patients being given adjuvant chemotherapy. Setting the NPI at a threshold of 4.4, 39% of patients would have been selected for treatment, while the OPI set at a threshold of 2.5 would result in 34% of patients being treated.

Table 7 and Figure 4 show these data in terms of incremental cost-effectiveness, with the current protocol set as the comparator. In comparison to the current protocol, using the NPI with a cut-off value of 4.4 would give less health benefit at higher cost, while using the OPI at a cut-off value of 2.5, or the actual treatment decisions taken, are estimated to have given less health benefit but at lower cost. Treating everyone would have given more health benefit than the current protocol but at a relatively high incremental cost-effectiveness ratio of over £45,000 per QALY gained. Treating only if a net gain in quality adjusted life expectancy is anticipated gives the greatest health benefit of all options considered, at an incremental cost-effectiveness ratio of £34,000 per QALY gained. Finally, making adjuvant chemotherapy decisions on the basis of anticipated cost-effectiveness, with a ceiling ratio of £30,000 per QALY gained, gives more health benefit than the current protocol and has a relatively low incremental cost-effectiveness ratio of just over £14,000 per QALY gained.

Variations in cut-off values used to make treatment selections

Figure 5 shows the effect of altering the threshold values of the NPI between 3 and 5, the OPI between 1 and 3.5, and cost-effectiveness ceiling between £0 and £40,000 per QALY when deciding who to offer adjuvant chemotherapy, and of increasing the threshold for net quality adjusted life expectancy gain from 0 to 0.5 (i.e., treat only if net gain in health is at least 0.5 quality adjusted life years). In each case the incremental costs and effects are plotted on the cost-effectiveness plane against the comparator of the current protocol.

The OPI gives a net gain in health outcome compared to the current protocol when the threshold value is lowered to approximately 1.8 from the baseline of 2.5. The NPI gives a net gain in health outcome compared to the current protocol when the threshold value for treatment is reduced from the baseline value of 4.4 to 4.3 or lower, but the incremental cost-effectiveness is high. When the cost-utility ceiling is reduced to approximately £13,570 per QALY it becomes cost saving relative to the current protocol, but below £10,250 per QALY it gives less health benefit. Altering the QALE gain threshold traces the same points as the cost per QALY sensitivity: when the decision rule is to treat as long as any health gain is obtained, this is equivalent to an infinite willingness to pay. Treating only when at least 0.5 quality adjusted life years are expected to be gained is equivalent to setting a cost-effectiveness threshold at approximately £22,500 per QALY gained.

Predictive performance of different criteria

Table 8 reports the sensitivity and specificity of different treatment selection criteria compared to cost-effectiveness criteria, using which (at a ceiling value of £30,000 per QALY gained) a total of 526 patients would have been selected for treatment. The actual treatment decisions made for these patients resulted in the lowest number being selected for chemotherapy: 273 of the 1058 patients. Both actual treatment decisions and the current Oxford protocol had a high specificity and high positive predictive value. Using the net improvement in quality adjusted life expectancy criteria (equivalent to infinite willingness to pay for any health gain) resulted in the highest number of patients being selected for treatment: 949.

Further Research

Given the apparent uncertainty as to which patients should and should not receive adjuvant chemotherapy in the UK, we plan to use the model to assess the cost-effectiveness of using other UK breast cancer protocols to select women for such treatment. The model does not currently allow for the costs of obtaining the prognostic information for use in decision-making. Costs associated with measurement of oestrogen receptor status, assessment of lymph node involvement, and tumor grade and size measurement etc. need therefore to be included. With regard to the structure of the model per se, future refinements may be carried out e.g. to take a more realistic account of relapse - at present it is simply assumed that relapse only occurs prior to a breast cancer death. Finally we would like to apply our model to other patient level datasets which exist in this area.

Conclusions

Decisions about how to use prognostic information or other criteria to guide treatment decisions for women with early breast cancer appear to be associated with quite different levels of cost-effectiveness. The use of expected individual cost-effectiveness ratios to guide treatment decisions and protocols is a promising approach and worthy of further examination in this and other treatment areas.

References

1. Calvert NW, Morgan AB, Catto JWF et al. Effectiveness and cost-effectiveness of prognostic markers in prostate cancer. *British Journal of Cancer* 2003; 88: 31-35.

2. Littrup PJ, Kane RA, Mettlin CJ et al. Cost-Effective Prostate Cancer Detection. Reduction of Low-Yield Biopsies. *Cancer* 1994; 74 (12): 3146-3158.

3. Mason JM, Drummond MF, Bosanquet AG et al. The DiSC ASSAY. A Cost-effective Guide to Treatment for Chronic Lymphocytic Leukemia? *International Journal of Technology Assessment in Health Care* 1999; 15 (1): 173-184.

4. Glance LG, Osler T, Shinozaki T. Intensive care unit prognostic scoring systems to predict death: A cost-effectiveness analysis. *Critical Care Medicine* 1998; 26 (11): 1842-1849.

5. Hamel MB, Phillips RS, Davis RB et al. Outcomes and Cost-Effectiveness of Initiating Dialysis and Continuing Aggressive Care in Seriously Ill Hospitalised Adults. Annals of Internal Medicine 1997; 127 (3): 195-201.

6. DoH 2002 NHS Cancer Screening Programmes. National Health Service Website: www. cancerscreening.nhs.uk

7. Bray F, Sankila R, Ferlay J et al. Estimates of cancer incidence and mortality in Europe in 1995. *European Journal of Cancer* 2002; 38 (1): 99-166.

8. Haybittle JL, Blamey RW, Elston CW. A prognostic Index in Primary Breast Cancer. *British Journal of Cancer* 1982; 45: 361-366.

9. Todd JH, Dowle C, Williams MR et al. Confirmation of a prognostic index in primary breast cancer. *British Journal of Cancer* 1987; 56: 489-492.

10. Early Breast Cancer Trialists' Collaborative Group. Tamoxifen for early breast cancer: an overview of the randomised trials. *Lancet* 1998; 351: 1451-1467.

11. GAD 2002. Interim Life Tables for England and Wales, women based on the years 1999-2001. Government Actuary's Department. Website: www.gad.gov.uk/Life_Tables/Interim_Life_Tables.htm

12. Early Breast Cancer Trialists' Collaborative Group. Polychemotherapy for early breast cancer: an overview of the randomised trials. *Lancet* 1998; 352: 930-942.

13. UK Treasury. Green Book, Appraisal and Evaluation in Central Government. Website: http://greenbook.treasury.gov.uk/chapter05.htm#discounting

14. British Medical Association and the Royal Pharmaceutical Society of Great Britain. The British National Formulary. Number 44. Wallingford: British Medical Association and the Royal pharmaceutical Society of Great Britain, 2003.

15. Karnon J and Brown J. Tamoxifen Plus Chemotherapy versus Tamoxifen Alone as Adjuvant Therapies for Node-Positive Postmenopausal Women with Early Breast Cancer. A Stochastic Economic Evaluation. *Pharmacoeconomics* 2002; 20 (2): 119-137.

16. Cocquyt V, Moeremans K, Clarys P et al. Postmenopausal breast cancer: incidence-based cost of illness. *Journal of Medical Economics* 2003; 6: 15-30.

Table 1: Initial variable list and missing information

Variable	Valid observations	No. (percent) missing
Patient identifier	1174	0 (0)
Date of Birth	1173	1 (0.1)
Age in years at operation	1173	1 (0.1)
Date of first operation	1174	0 (0)
Estrogen Receptor level	832	342 (29.1)
Grade (ductal) using Bloom & Richardson system	1173	1 (0.1)
Tumour size	1117	54 (4.9)
Number of nodes sampled	1165	9 (0.8)
Number of nodes positive	1145	29 (2.5)
Adjuvant Chemotherapy used	1167	7 (0.6)
Adjuvant radiotherapy used	1170	4 (0.3)
Adjuvant hormone therapy used	1168	6 (0.5)
Relapse	1174	0 (0)
Time to death or censored	1171	3 (0.3)

Table 2: Summary of patient and clinical characteristics for 1,058 women in the Oxford dataset.

Variable	
Age in years - Mean (SD)	56.6 (11.7)
Tumour grade	
Grade 1 (Good) n (%)	210 (20)
Grade 2 (Moderate) n (%)	484 (46)
Grade 3 (Poor) n (%)	364 (34)
Tumour size in cm – Mean (SD)	2.4 (1.34)
Nodal involvement	
0 nodes n (%)	625 (59)
1-3 nodes n (%)	300 (28)
≥ 4 nodes n (%)	133 (13)
ER status	
Positive	767 (72)
Negative	291 (28)
Adjuvant Therapies	
Chemotherapy (alone or in combination) n (%)	273 (26)
Hormone (alone or in combination) n (%)	781 (74)
Radiotherapy (alone or in combination) n (%)	885 (84)
Outcomes	
Relapse n (%)	312 (29)
Time to relapse in years - Mean	3.24
Deaths n (%)	311 (29)
Time to death in years - Mean	4.16

Table 3 – Coefficients estimated from survival analysis using a simple exponential model of constant hazard

Explanatory Variable	Coefficient.	SE	P-value
ageatop	0.031791		
tumoursize	0.185175		
tumourstage2	0.577657		
tumourstage3	1.361642		
tumourgrade2	0.379655		
tumourgrade3	0.933166		
adjchemo	-0.10918		
adjhormone	-0.20215		
opyear~1996	-0.92151		
ERstatus	-0.44553		
predER	-0.0857		
constant	-11.55		

Table 4 Effect of adjuvant chemotherapy and hormone treatment on the relative risk of breast cancer death(*? Or recurrence)

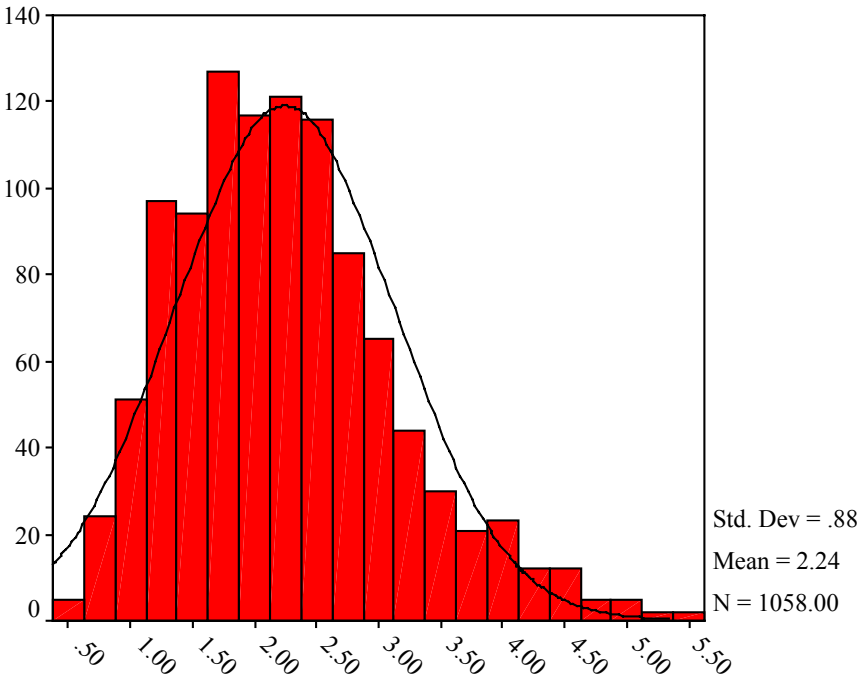
	Hormone Treatment	**Control**	**Relative risk of treatment compared to control**
ER'-'ve	0.408	0.374	1
ER'+'ve	0.221	0.28	0.76
	Chemotherapy Treatment	**Control**	**Relative risk of treatment compared to control**
Age <50	0.323	0.394	0.78
Age 50-59	0.352	0.385	0.89
Age >60	0.357	0.38	0.92

Source: * EBCTG

Table 5: Cost, utility and probability parameters used in cost-effectiveness model, with sources of information

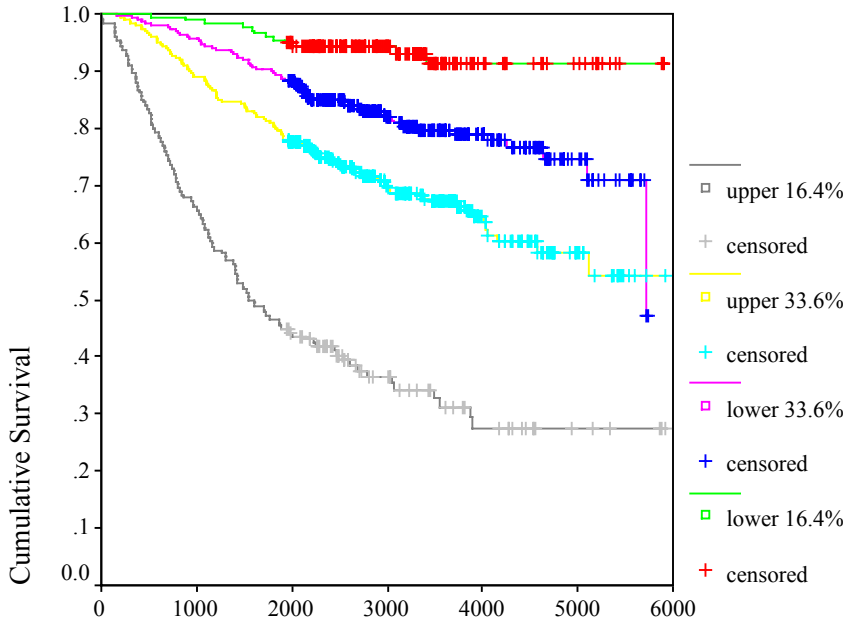
Variable	Value	Description	Source
Discounting			
cDR	0.03	cost discount rate	UK Treasury
oDR	0.03	outcome discount rate	UK Treasury
Treatment cost			
hormC	136.26	Hormone treatment cost	BNF 44 / 20mg daily dose / duration 5 years
chemoC	2000	Adjuvant chemotherapy cost	Clinical opinion / Karnon & Brown ABC paper Pharmacoeconomics 2002; 20 (2)
Side effect probabilities			
hormSEp	0.05	Probability of side-effects from hormone Tx	Clinical opinion / Karnon & Brown ABC paper Pharmacoeconomics 2002; 20 (2)
chemoSEp	0.3	Probability of side-effects from chemotherapy Tx	Clinical opinion / Karnon & Brown ABC paper Pharmacoeconomics 2002; 20 (2)
Side effect utility decrements			
hormSEud	0.25	Utility decrement associated with having side-effects from hormone Tx	Informed by Karnon & Brown ABC paper Pharmacoeconomics 2002; 20 (2)
chemoSEud	0.25	Utility decrement associated with having side-effects from chemotherapy Tx	Informed by Karnon & Brown ABC paper Pharmacoeconomics 2002; 20 (2)
Side effect treatment costs			
hormSEc	1982	Cost of treating side-effects of hormone Tx	Weighted average of tamoxifen grade 3/4 toxicity and major toxicity costs from Karnon & Brown ABC paper Pharmacoeconomics 2002; 20 (2)
chemoSEc	700	Cost of treating side-effects of chemotherapy Tx	Weighted average of tamoxifen plus chemo grade 3/4 toxicity and major toxicity costs from Karnon & Brown ABC paper Pharmacoeconomics 2002; 20 (2)
Relapse			
relapseUD	0.35	Utility decrement associated with breast cancer relapse	Assumes locoregional relapse from Karnon and Brown ABC paper Pharmacoeconomics 2002; 20 (2)
relapseCost	10520	Cost associated with breast cancer relapse	Cocquyt V et al. Journal of Medical Economics 2003: 6; 15-30.

Figure 1 Histogram showing distribution of OPI scores



OPI scores

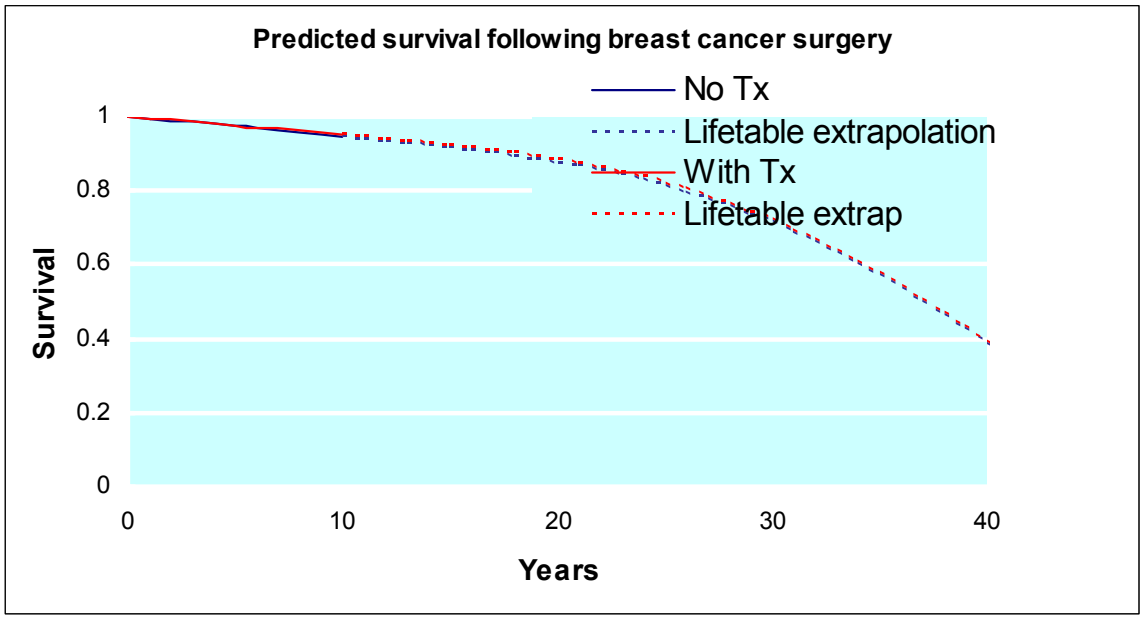
Figure 2: Survival curves for four prognostic groups based on the OPI



time to death or censoring (days)

Figure 3 : Predicted survival following breast cancer surgery assuming treatment or no treatment with adjuvant chemotherapy

(a)



(b)

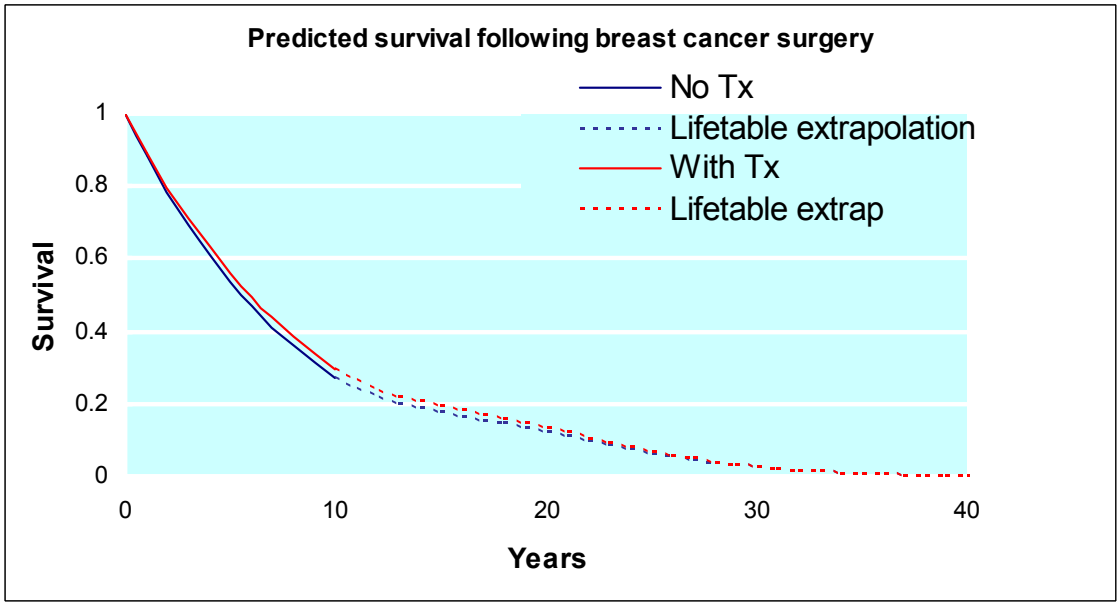


Table 6: Average costs and effects per patient of different prognostic criteria (sample = 1058 patients)

	Number (%) of patients selected for treatment	Average discounted quality adjusted life expectancy (years)	Average costs
Treat if NPI >4.4	411 (39%)	11.04	£3,402
Treat if OPI > 2.5	359 (34%)	11.01	£3,120
Treat if QALE >0	949 (90%)	11.09	£4,599
Treat if C-E < £30,000	569 (54%)	11.08	£3,509
Treat All	1058 (100%)	11.09	£4,857
Treat None	0 (0%)	10.92	£2,575
Actual treatment	273 (26%)	11.03	£3,105
Current protocol	371 (35%)	11.06	£3,298

Table 7: Incremental costs, effects and cost-effectiveness of different prognostic criteria compared to current protocol

	Incremental effect (QALYs)	Incremental cost	ICER
Treat by NPI	-18.40	£83,510	-
Treat by OPI	-52.43	-£10,909	-
Treat by QALE	35.31	£1,198,713	£33,944
Treat by C-E	28.28	£399,982	£14,141
Treat All	31.64	£1,432,021	£45,264
Treat None	-146.29	-£699,477	-
Actual treatment	-33.68	-£187,024	-

Figure 4: Incremental costs and effects of different prognostic methods compared to current protocol on the cost-effectiveness plane

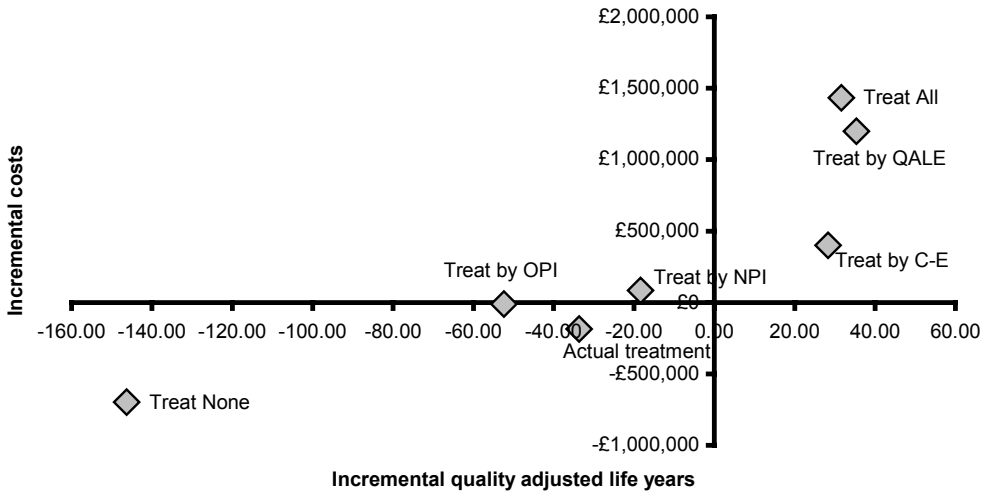


Figure 5: Sensitivity analysis of incremental costs and effects of different prognostic methods compared to current protocol when threshold/ceiling values are changed

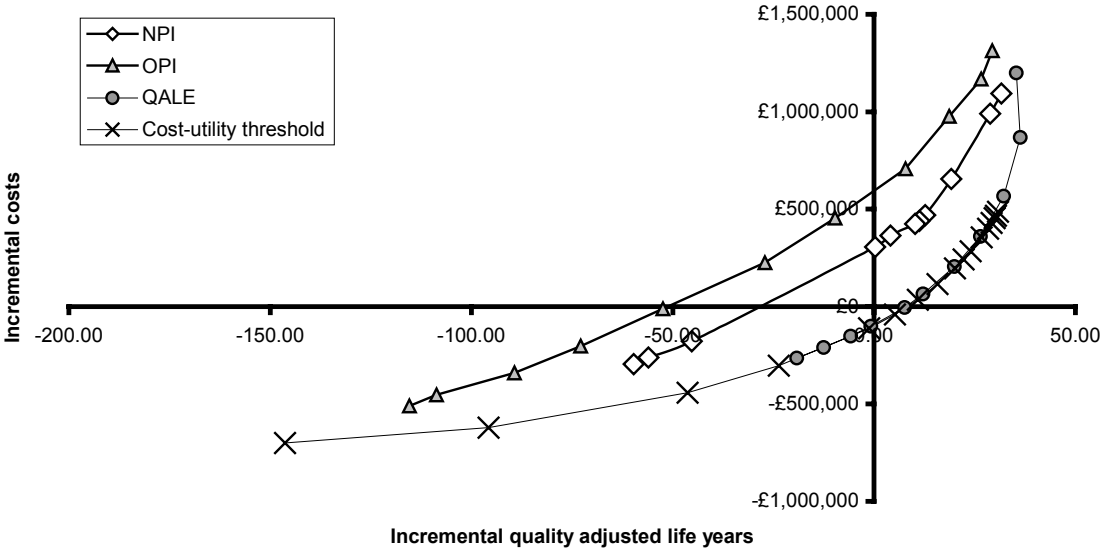


Table 8: Sensitivity, specificity and positive and negative predictive value different treatment selection criteria compared to cost-effectiveness criteria

	Sensitivity	Specificity	PPV	NPV	Number treated
NPI	56.9%	82.2%	78.8%	62.1%	411
OPI	43.2%	76.9%	68.5%	53.8%	359
QALE	100.0%	22.3%	60.0%	100.0%	949
Actual	45.5%	97.1%	94.9%	60.5%	273
Current protocol	63.8%	98.4%	97.8%	70.0%	371