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The cost-effectiveness of adjuvant chemotherapy for early breast cancer: A comparison of no chemotherapy and first, second, and third generation regimens for patients with differing prognoses ☆

H.E. Campbell [a,*], D. Epstein [b], D. Bloomfield [c], S. Griffin [b], A. Manca [b], J. Yarnold [d], J. Bliss [e], L. Johnson [e], H. Earl [f], C. Poole [g], L. Hiller [h], J. Dunn [h], P. Hopwood [e], P. Barrett-Lee [i], P. Ellis [j], D. Cameron [k], A.L. Harris [l], A.M. Gray [a], M.J. Sculpher [b]

[a] Health Economics Research Centre, University of Oxford, Headington, Oxford, OX3 7LF, United Kingdom
[b] Centre for Health Economics, University of York, Heslington, York, YO10 5DD, United Kingdom
[c] Sussex Cancer Centre, Brighton & Sussex University Hospitals, Brighton, BN2 5BE, United Kingdom
[d] Royal Marsden NHS Trust, London and Sutton, United Kingdom
[e] ICR-CTSU, Section of Clinical Trials, The Institute of Cancer Research, Sutton, Surrey, SM2 5NG, United Kingdom
[f] University of Cambridge, Department of Oncology, NIHR Cambridge Biomedical Research Centre, Cambridge, CB2 0QQ, United Kingdom
[g] University of Warwick, Warwick, Coventry, CV4 7AL, United Kingdom
[h] Warwick Medical School Clinical Trials Unit, University of Warwick, Coventry, CV4 7AL, United Kingdom
[i] Velindre Cancer Centre, Velindre Hospital, Cardiff, CF14 2TL, United Kingdom
[j] Guys and St Thomas NHS Foundation Trust, Cancer Management Office, Guys Hospital, London, SE1 9RT, United Kingdom
[k] Edinburgh Cancer Research Centre, Western General Hospital, Edinburgh, EH4 2XR, United Kingdom
[l] Cancer Research UK Medical Oncology Department, Churchill Hospital, Headington, Oxford, OX3 7LJ, United Kingdom

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ABSTRACT

Background: The risk of recurrence following surgery in women with early breast cancer varies, depending upon prognostic factors. Adjuvant chemotherapy reduces this risk; however, increasingly effective regimens are associated with higher costs and toxicity profiles, making it likely that different regimens may be cost-effective for women with differing prognoses. To investigate this we performed a cost-effectiveness analysis of four treatment strategies: (1) no chemotherapy, (2) chemotherapy using cyclophosphamide, methotrexate, and fluorouracil (CMF) (a first generation regimen), (3) chemotherapy using Epirubicin-CMF (E-CMF) or fluorouracil, epirubicin, and cyclophosphamide (FEC60) (a second generation regimens), and (4) chemotherapy with FEC60 followed by docetaxel (FEC-D) (a third generation regimen). These adjuvant chemotherapy regimens were used in three large UK-led randomised controlled trials (RCTs).

Methods: A Markov model was used to simulate the natural progression of early breast cancer and the impact of chemotherapy on modifying this process. The probability of a first recurrent event within the model was estimated for women with different prognostic risk profiles using a parametric regression-based survival model incorporating established

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* *Corresponding author:* Address: Health Economics Research Centre, Department of Public Health, University of Oxford, Old Road Campus, Headington, Oxford, OX3 7LF, United Kingdom. Tel.: +44 1865 289274; fax: +44 01865 289271.
E-mail address: helen.campbell@dph.ox.ac.uk (H.E. Campbell).

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prognostic factors. Other probabilities, treatment effects, costs and quality of life weights were estimated primarily using data from the three UK-led RCTs, a meta-analysis of all relevant RCTs, and other published literature. The model predicted the lifetime costs, quality adjusted life years (QALYs) and cost-effectiveness of the four strategies for women with differing prognoses. Sensitivity analyses investigated the impact of uncertain parameters and model assumptions.

Findings: For women with an average to high risk of recurrence (based upon prognostic factors and any other adjuvant therapies received), FEC-D appeared most cost-effective assuming a threshold of £20,000 per QALY for the National Health Service (NHS). For younger low risk women, E-CMF/FEC60 tended to be the optimal strategy and, for some older low risk women, the model suggested a policy of no chemotherapy was cost-effective. For no patient group was CMF chemotherapy the preferred option. Sensitivity analyses demonstrated cost-effectiveness results to be particularly sensitive to the treatment effect estimate for FEC-D and the future price of docetaxel.

Interpretation: To our knowledge, this analysis is the first cost-effectiveness comparison of no chemotherapy, and first, second, and third generation adjuvant chemotherapy regimens for early breast cancer patients with differing prognoses. The results demonstrate the potential for different treatment strategies to be cost-effective for different types of patients. These findings may prove useful for policy makers attempting to formulate cost-effective treatment guidelines in the field of early breast cancer.

1. Introduction

For women with early breast cancer, surgery to remove the primary tumour is often followed by adjuvant chemotherapy, a combination of cytotoxic drugs given to reduce the risk of disease recurrence. Recent decades have seen major advances in chemotherapy treatment as new and potentially more effective classes of drugs and modes of administration are developed. Randomised controlled trials (RCTs) have evaluated first generation alkylating-based chemotherapy regimens, second generation anthracycline-based regimens and third generation taxane-based regimens.[1–5]

Health economic evaluation has been used to assess the cost-effectiveness of adjuvant chemotherapy regimens; most recently, those containing the taxane agents docetaxel and paclitaxel.[6–9] However, these evaluations, and the RCTs providing the corresponding clinical data, conducted pair-wise comparisons in which the new generation therapy was assessed only against the previous generation's therapy. To our knowledge, no clinical or economic assessment has to date simultaneously compared all potential adjuvant chemotherapy treatment strategies; that is, first, second, and third generation regimens, as well as a policy of using no adjuvant chemotherapy. A simultaneous comparison of this kind would prove informative for several reasons. Firstly, there has been considerable recent research on the effectiveness of all adjuvant chemotherapies, including meta-analyses conducted by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) and systematic reviews by the Cochrane Breast Cancer Group.[1,10] This evidence should inform and update economic analysis and policy. Secondly, there are factors relating to the progression and treatment of early breast cancer that mean different chemotherapy regimens may be cost-effective for different patient groups. The risk of recurrence, for example, can vary substantially between women depending upon prognostic factors including age, axillary lymph node status, and tumour grade, size, and oestrogen receptor (ER) status.[11–13] Also, the proportional reduction in the risk of recurrence with chemotherapy is known to vary by age, and women with ER positive tumours now routinely receive adjuvant anti-hormone therapy, which also reduces the risk of recurrence, but independently of chemotherapy.[1] Finally, advances in treatment effectiveness come at a cost, as new chemotherapy regimens are usually more expensive than older regimens and potentially more toxic, resulting in an increase in adverse events and a detrimental impact on patient health related quality of life (HRQoL). Given all of these factors, it would appear important to review each of the relevant treatment options for all types of patient.

This paper describes a cost-effectiveness analysis in which the lifetime costs and quality adjusted life years (QALYs) (life years adjusted for HRQoL) of adjuvant chemotherapy treatment options for women with early breast cancer are estimated and compared. Reflecting the full range of management options which have been used in the adjuvant setting in United Kingdom trials over recent years, the strategies considered are:

I. no chemotherapy,
II. first generation chemotherapy with CMF (six cycles of cyclophosphamide, methotrexate, fluorouracil),
III. second generation chemotherapy with FEC60 (eight cycles of fluorouracil, epirubicin, cyclophosphamide) or E-CMF (four cycles of epirubicin followed by four cycles of CMF), and
IV. third generation chemotherapy with FEC-D (four cycles of FEC60 followed by four cycles of docetaxel).

These chemotherapy regimens are defined in accordance with the protocols of three pragmatic UK-led RCTs – the Adjuvant Breast Cancer (ABC) Trial which began in 1992 and compared CMF with no chemotherapy, the National Epirubicin

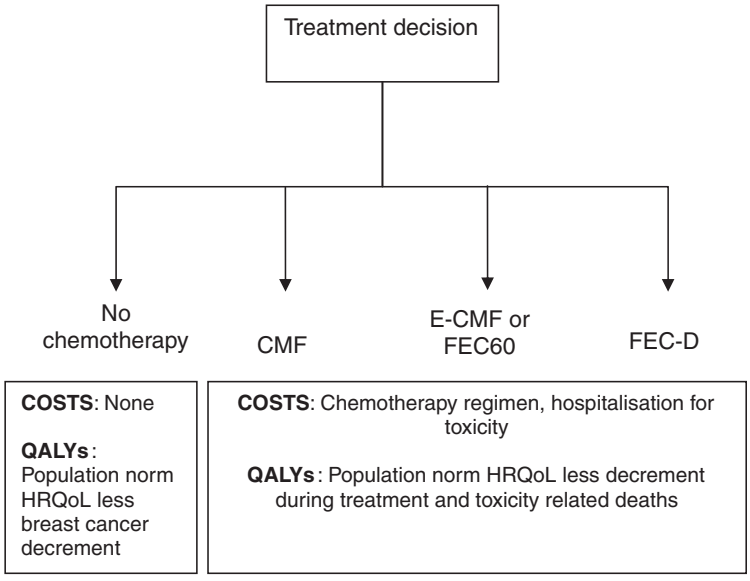
Adjuvant Trial (NEAT) which began in 1996 and compared E-CMF with CMF, and the Taxotere as Adjuvant Chemotherapy Trial (TACT) which began in 2001 and compared FEC-D with FEC60 or E-CMF.[3–5] Docetaxel is not currently licensed in the UK for use as a single agent following FEC. This regimen is, however, advocated by the majority of breast cancer oncologists in the UK and indeed worldwide, because when used on its own, docetaxel carries a lower risk of adverse events than if used simultaneously with other agents.[14] In line with the TACT trial protocol and indirect evidence from the trial results, our analysis assumes equivalence of FEC60 and E-CMF in terms of effectiveness and toxicity.

2. Methods

2.1. *Overview and model structure*

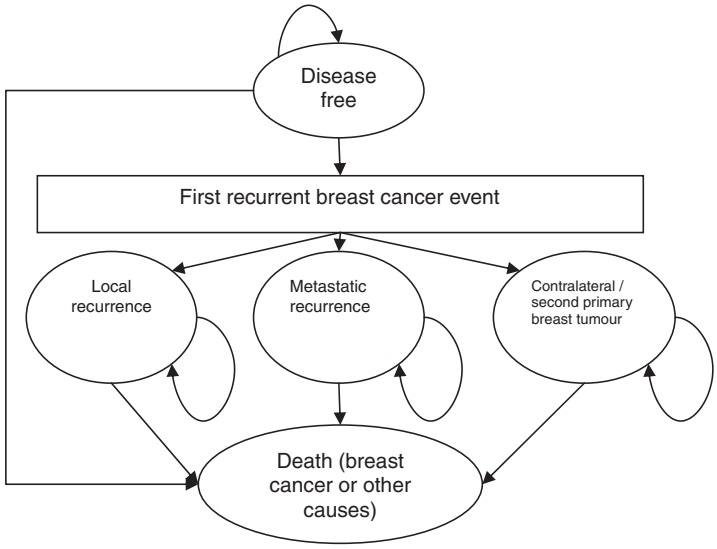
The analysis followed the methodological guidelines from the National Institute of Health and Clinical Excellence (NICE).[15] It was conducted from a UK National Health Service (NHS) perspective and the annual discount rate used for costs (expressed as 2009 Pound Sterling) and effects was 3.5%.[16] Fig. 1 shows the structure of the economic model. Following local surgery, (a hypothetical cohort of) patients enter a short term decision tree (panel a) and are assigned to one of the

Panel A: decision tree for first 6 months of the analysis



HRQoL – Health related quality of life

Panel B: long term Markov model*



*Models with this structure are attached to each of the four branches in the decision tree.

Fig. 1 – Model structure.

four treatment options being compared. During the first 6 months (the average duration of chemotherapy) they are assumed to be free from breast cancer. Patients receiving chemotherapy incur treatment costs and face the risk of regimen-specific toxicity which may culminate in death, hospitalisation and/or reduced HRQoL.

In month seven, patients enter the Markov model (panel b) which simulates the natural progression of the disease, and the impact of chemotherapy on modifying this process. The model comprises a set of mutually exclusive health states, which patients can move between at annual intervals according to transition probabilities. Values are attached to each health state in the model to reflect the cost and HRQoL associated with a year spent in that state. Patients then accrue costs and QALYs according to their health state in the model during each year.

Following chemotherapy, surviving patients enter the 'disease free' health state of the model where they remain until experiencing a first recurrent breast cancer event (which can be local, metastatic, or a contralateral/second primary breast tumour) or death from causes unrelated to breast cancer. Patients transiting to a recurrence health state remain there until they die from breast cancer or another cause. Although further recurrent events experienced prior to a breast cancer death (for example a metastatic recurrence following a local recurrence) are not explicitly modelled with additional health states (this would over-complicate the model's structure), their consequences are still captured within the analysis through the cost and HRQoL values assigned to the existing recurrence health states. The model was developed and run in Excel 2007 (Microsoft Corporation, Redmond, WA, United States of America).

2.2. Populating the model

Parameters were estimated using individual patient data collected as part of the ABC, NEAT, and TACT trials, and from administrative datasets, comprehensive searches of the published literature, and expert clinical opinion. Abridged detail is given below, with more information available in the web appendices.

2.3. During chemotherapy

Based on individual patient data from the three trials, Table 1 presents the expected cost per patient of each chemotherapy regimen and of breast cancer related hospital admissions during chemotherapy. Informed by data collected during the ABC trial, women entering the model were assumed to have HRQoL on average equivalent to women in the age-matched UK general population. This is based on the EQ-5D instrument, a generic measure of HRQoL consisting of five dimensions (mobility, self care, usual activities, pain/discomfort, and anxiety/depression) on each of which the respondent indicates whether they have no problems, some problems or severe problems.[17] These responses are translated onto a valuation scale between 0 (equivalent to death) and 1 (equivalent to full health) based on the views of a sample of the UK public.[18] During chemotherapy, the decrements in HRQoL (again using the EQ-5D) were estimated for each regimen based on trial data (Table 1). Patients may die as a result of chemotherapy-related toxicity in the first 6 months. Across the three RCTs such deaths were rare and so a pooled probability of toxicity-related death was calculated and applied to all chemotherapy patients (Table 1).

2.4. After chemotherapy

2.4.1. Transition probabilities

Table 2 gives the transition probabilities used in the Markov model.

The underlying annual probability of a first recurrent event was derived from a published and validated parametric regression-based survival model (see web Appendix 1).[19] Risk

Table 1 – Mean per patient cost and HRQoL values used to populate the decision tree.[a]

Parameter	Value	Source
Costs		
CMF chemotherapy	£3,029	ABC,[39–42]
E-CMF/FEC60 chemotherapy	£3,576	TACT,[39–42]
FEC-D chemotherapy	£6,936	TACT,[39–42]
Breast cancer related hospital admissions during CMF	£90	NEAT,[43]
Breast cancer related hospital admissions during E-CMF/FEC60	£123	NEAT,[43]
Breast cancer related hospital admissions during FEC-D	£175	TACT,[43]
HRQoL based on the EQ-5D health instrument	Age and sex adjusted	[44]
Underlying HRQoL levels	United Kingdom population norms	
Decrement in HRQoL from underlying levels in		
Patients not receiving chemotherapy	–.003	ABC
Patients receiving CMF	–0.057	ABC
Patients receiving E-CMF/FEC60	–0.067	NEAT, TACT
Patients receiving FEC-D	–0.099	TACT
Probability of death from chemotherapy-related toxicity during 6 months of treatment	0.00371	ABC, NEAT, TACT

[a] Parameter estimates shown are based upon analyses of individual patient data collected during the three trials and are comprised of multiple components (costs) or are additive in nature (HRQoL decrements). Individual components and estimates of their associated uncertainty are given in web Appendix 1.

Table 2 – Parameter values used within the Markov model.

Parameter	Value	Source
Annual transition probabilities		
First recurrent event in the absence of hormone therapy and chemotherapy (predictions include radiotherapy) – years 1–50	Variable – dependent upon age, number of positive nodes, grade, size, and ER status of the primary tumour, and time since diagnosis	[19]
First recurrent event is local	0.227 (461/2028)	ABC, TACT, data from Churchill Hospital, Oxford
First recurrent event is metastatic	0.705 (1430/2028)	
First recurrent event is a contralateral/second primary breast tumour	0.068 (137/2028)	
Breast cancer death following recurrence – years 1–15 post recurrence	Variable – dependent upon type of recurrence and time since recurrence diagnosed	ABC, TACT, data from Churchill Hospital, Oxford
Breast cancer death following recurrence – years 16 and onwards post recurrence	4.7 times age adjusted UK breast cancer mortality rates	[20,22]
Death from causes other than breast cancer – years 1–50	Age and sex adjusted UK population norms	[21,22]
Relative treatment effect estimates for recurrence		
Tamoxifen versus no hormone therapy (ER positive women aged <50 years) – years 1–10	0.59 (SE = 0.03)	[1]
Aromatase inhibitor versus tamoxifen (ER positive women aged >50 years)[a] – years 1–10	0.74 (SE = 0.06)[d]	[45]
CMF versus no chemotherapy, women aged <50 years – years 1–10	0.59 (SE = 0.04)	[1]
CMF versus no chemotherapy, women aged >50 years – years 1–10	0.81 (SE = 0.03)	[1]
Anthracycline-based chemotherapy versus CMF[b] – years 1–10	0.89 (SE = 0.03)	[1]
FEC-D versus E-CMF/FEC60[c] – years 1–10	0.90 (SE = 0.05)	[2,3]
Unit costs (2009 UK £)		
Mammogram	£46.37 (SE = £9.27)	[42,46]
Outpatient clinic attendance	£99.00 (SE = £19.80)	[43]
Local recurrence – year 1	£13,898 (SE = £2,388)[d]	[24,42]
Local recurrence – years 2–5	£1,235 (SE = £428)[d]	[24,42]
Contralateral/second primary breast tumour – year 1	£18,374 (SE = £4,750)[d]	[24,42]
Contralateral/second primary breast tumour – years 2–5	£586 (SE = £101)[d]	[24,42]
Metastatic recurrence – year 1	£10,482 (SE=£1,135)[d]	[24,42]
Metastatic recurrence – year 2	£8,609 (SE = £1,354)[d]	[24,42]
Metastatic recurrence – year 3	£4,811 (SE = £1,506)[d]	[24,42]
Metastatic recurrence – year 4	£2,276 (SE = £886)[d]	[24,42]
Metastatic recurrence – year 5	£2,274 (SE = £804)[d]	[24,42]
End of life care (3 months prior to breast cancer death)	£4,038 (SE = £454)[d]	[24,42]
HRQoL		
Underlying level of HRQoL	Population norms	[44]
Decrement in HRQoL with CMF – year 1[e]	–0.057	ABC
Decrement in HRQoL with E-CMF/FEC60 – year 1[e]	–0.038	NEAT, TACT
Decrement in HRQoL with FEC-D – year 1[e]	–0.035	TACT
Decrement in HRQoL with local recurrence	–0.108 (SE = 0.04)	[47–50]
Decrement in HRQoL with metastatic recurrence	–0.303 (SE = 0.16)	[48,51–54]
Decrement in HRQoL with contralateral/second primary breast tumour	–0.108 (SE = 0.04)	[47–50]
HRQoL in final 3 months of life	0.159 (SE = 0.04)	[52,55–57]

[a] Treatment effect for aromatase inhibitor is for anastrazole and is taken from the ATAC trial.[45]

[b] Used in this analysis as effectiveness estimate for E-CMF/FEC60.

[c] The hazard ratio for FEC-D versus E-CMF/FEC60 is pooled from the TACT and PACS01 trials and is for disease free survival (recurrence plus death from any cause) rather than just recurrence. Given the small number of deaths from treatment-related toxicity, and an expectation that deaths from other causes would be equally distributed across both arms of the TACT and PACS01 trials, we assume the ratio for DFS is a reasonable proxy for the ratio for first recurrence, the parameter used in the model.

[d] Standard error inferred from 95% confidence intervals.

[e] HRQoL decrements in the year following chemotherapy are additive in nature. Individual components and estimates of their associated uncertainty are given in web Appendix 1.

of recurrence was predicted on the basis of a patient's age, number of positive axillary lymph nodes, the grade, size, and ER status of the primary tumour, assuming radiotherapy is given. The predictions are time dependent, to reflect the increasing risk of recurrence in the first 2 years after breast cancer surgery and the decreasing risk thereafter. Following the prediction of a first recurrent event in a given year, patients are distributed across the Markov model's three recurrence health states according to the proportions shown in Table 2.

The annual risk of breast cancer death following each type of first recurrent event was estimated using a second parametric regression-based survival model (see web Appendix 1). This model was estimated using patient data from a number of sources and is time dependent to allow for the increasing mortality risk in the first 3–4 years after recurrence, and a declining risk thereafter. It was used to predict the probability of breast cancer death for the first 15 years after each type of recurrence. Thereafter the risk of death following breast cancer was based on the rate for the UK general population inflated by a factor of 4.7 as observed for long term breast cancer survivors (see Table 2).[20]

Finally, deaths from causes other than breast cancer were accounted for in the model by applying age and sex adjusted UK life table data (excluding breast cancer deaths) to all non-terminal health states.[21,22]

2.4.2. *Treatment effects*

Table 2 shows the treatment effect estimates, in the form of hazard ratios, used to adjust the underlying annual risk of a recurrent event in the first 10 years in the model. As per clinical practice (and independent of any chemotherapy modelled) pre-menopausal women with ER positive tumours were assumed to receive 5 years of tamoxifen and post-menopausal ER positive women 5 years with an aromatase inhibitor (see Table 2). Estimates of the effectiveness of CMF and E-CMF/FEC60 regimens were taken from the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analyses; for FEC-D estimates were taken from a pooled analysis of data from the only two trials to have compared the sequential use of docetaxel with an anthracycline-based comparator of a similar duration (TACT and PACS 01).[1–3] The effect of each type of chemotherapy was on the risk of recurrence, and for E-CMF/FEC60 and FEC-D, was estimated indirectly by assuming hazard ratios were additive on the log scale (see Fig. 2). In line with the published literature, the model employed separate chemotherapy treatment effect estimates for women above and below the age of 50.[1]

2.4.3. *Costs*

Patients who remained in remission or survived more than 5 years following a local or contralateral recurrence or second primary tumour were assumed to undergo mammographic surveillance and outpatient follow-up according to NICE guidelines.[23] The unit costs applied to these contacts are shown in Table 2.

A published costing study was used as the source of annual costs of treating each type of recurrence for 5 years and for an estimate of the cost of terminal care which was assigned to patients in the model 3 months prior to a breast cancer death (see Table 2).[24] Patients in that study are likely to be representative of patients in the ABC, NEAT and TACT

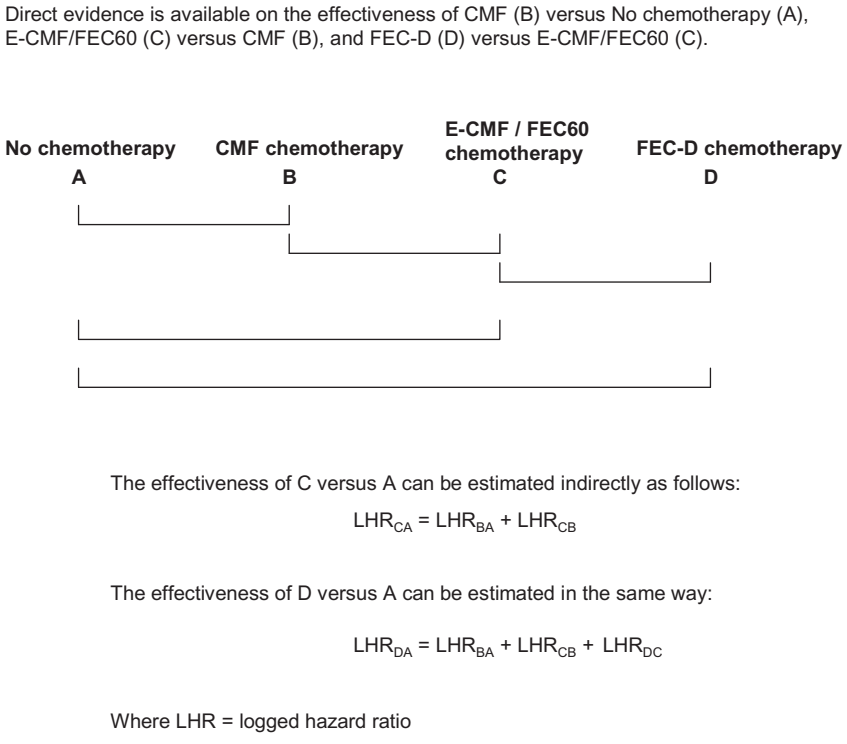


Fig. 2 – Indirect estimation of the effect of E-CMF/FEC60 and FEC-D upon the underlying risk of recurrence.[38]

trials, having been treated at a UK oncology department that recruited patients to all three of these studies. For patients with a local recurrence or a contralateral/second primary breast tumour and who died from breast cancer at the end of a year, metastatic disease was assumed to have been diagnosed half-way through that year, and related treatment costs (and HRQoL decrements – see below) applied.

2.4.4. HRQoL

Data collected from ABC, NEAT, and TACT suggested the negative impact of chemotherapy on HRQoL continues for up to a year following treatment in patients who remain recurrence free (see Table 2). HRQoL decrements applied to patients in the recurrence health states of the model and in the 3 months preceding a breast cancer death were informed by a review of published literature (see Table 2 and web Appendix 1).

2.5. Cost-effectiveness

The time horizon for the analysis, including the first 6 months in the decision tree, was 50.5 years. The discounted costs and QALYs accrued by patients during these years were summed to give an estimate of expected lifetime costs and effects with each treatment strategy. All strategies were then compared and those that were dominated (i.e. more costly but no more effective than another strategy or a combination of other strategies) were excluded. Remaining strategies were ranked in increasing order of effectiveness and incremental cost effectiveness ratios (ICERs) computed.[25] The ICER provides an estimate of the additional cost of generating one additional QALY, and is calculated as the difference in cost divided by the difference in QALYs between a treatment and its next best alternative. These ICERs were compared against the cost effectiveness threshold, which, in the case of NICE in the UK, lies between £20,000 and £30,000 per QALY and seeks to reflect the health foregone when new interventions are funded and displace existing services.[15] The most effective strategy with an ICER below this threshold is considered most cost effective.

For every level of prognosis, the potential exists for a range of cost-effectiveness results depending upon the age (which determines the magnitude of chemotherapy effectiveness) and ER status (which determines the use of anti-hormone therapy) of the patient. For this reason a definitive 'base-case' result is not presented. Rather, cost-effectiveness is first estimated for a cohort of younger (age 40) ER negative women. The number of positive nodes (1), tumour grade (2), and tumour size (3 cm) for this cohort were selected so that, together with age and ER status, they generated a baseline prognosis prediction equivalent to that of the 'average risk' patient in the ABC trial, where the probability of remaining recurrence free out to 10 years in the absence of chemotherapy and anti-hormone therapy (as predicted by the model on the basis of prognostic factors and assuming radiotherapy is given) was estimated to be around 44%. In a series of sub-group analyses, the impact of increasing the age and changing the ER status of this 'reference-case' cohort is explored.

2.6. Sub-group analyses

The age of the reference-case cohort was increased from 40 to 60 to assess the impact of reduced chemotherapy effectiveness in older women. In both of these age groups ER status was also switched from negative to positive, and the assumption made was that younger women would receive 5 years of tamoxifen and older women 5 years of an aromatase inhibitor. Additional analyses were conducted for patients considered 'high risk' and 'low risk' for recurrence based upon the following prognostic factor profiles. High risk women were assumed to be aged 40, with four positive lymph nodes, and an ER negative grade 3 tumour 4 cm in diameter. On the basis of these factors and assuming radiotherapy to be given, the baseline prognosis for this group (i.e. the predicted probability of remaining recurrence free at 10 years in the absence of chemotherapy (and, given the negative ER status of the group, anti-hormone therapy)), was estimated to be 18%. Low risk women were assumed to be aged 40, to be axillary lymph node negative, and with an ER positive grade 1 tumour 2 cm in diameter. On the basis of these factors and again assuming radiotherapy to be given, baseline prognosis (i.e. the predicted probability of remaining recurrence free at 10 years in the absence of chemotherapy (but, given the positive ER status of the group, in the presence of 5 years of tamoxifen)), was estimated to be 85%. Analyses exploring changes to the age of patients in these high and low risk groups were also conducted.

Given the impracticalities of reporting detailed results for large numbers of differing prognostic groups, the sub-group analyses provide an insight into how the cost-effectiveness of chemotherapy differs between patient groups at opposite ends of the risk spectrum. ICERs from the model were,

Table 3 – Expected discounted lifetime costs (2009 £ UK) and QALYs for each of the four treatment strategies modelled based on the reference case cohort.[a]

	No chemotherapy	CMF chemotherapy	E-CMF/FEC60 chemotherapy	FEC-D chemotherapy
Costs				
Chemotherapy[b]	–	£3,113	£3,691	£7,111
Routine follow-up[c]	£1,087	£1,220	£1,245	£1,264
Recurrence	£13,116	£10,743	£10,310	£9,952
Total costs	£14,204	£15,076	£15,246	£18,327
Total QALYs	10.93	12.35	12.66	12.88

[a] Patient is age 40, with one positive node, and a grade 2, ER negative tumour 3 cm in diameter.
[b] Includes chemotherapy drug and toxicity costs.
[c] Costs incurred in disease free health state.

however, also plotted against predicted baseline risk to illustrate how the most cost-effective strategy changes as a function of the risk of recurrence.

2.7. Sensitivity analysis

Model parameters were assigned probability distributions to describe the range of plausible values they could take based on the precision of the source evidence (for further details see web Appendix 1). Probabilistic sensitivity analysis (PSA) was then conducted to examine the joint impact of all uncertain parameters in the model upon cost-effectiveness results.[26–28] By running the model 3000 times, each time randomly sampling a set of plausible values from the parameter distributions and recalculating the results, it was possible to describe the strength of evidence in favour of each treatment strategy being most cost-effective. Results are presented by describing, for a range of different cost-effectiveness thresholds, the probability that a strategy is cost-effective.

One-way sensitivity analysis was used to assess the impact on cost-effectiveness results of changes in individual model parameters and assumptions. Amongst the analyses conducted (see column 1 of Table 4 for details) were assessments of the sensitivity of the model's results to the use of time dependent chemotherapy treatment effects, alternative durations of chemotherapy treatment effect, and an assumption that HRQoL returns to general population levels in

Table 4 – Scenarios modelled in sub-group / one-way sensitivity analyses. Shown are associated ICERs for each treatment strategy compared with the next best alternative (the first strategy in the column to the left which is not dominated)

	ICER (Probability that strategy is cost-effective at £20,000 per QALY[a])			
	No chemotherapy	CMF chemotherapy	E-CMF/FEC60 chemotherapy	FEC-D chemotherapy
Reference-case results				
Average risk woman aged 40 years and ER negative[b]	–(0)	Dom (0)	£603 (0.28)	£13,704 (0.72)
Sub-group analyses				
Average risk altering age and ER status				
Average risk woman aged 60 years and ER negative[b]	–(0)	Dom (0)	£4,172 (0.46)	£18,550 (0.54)
Average risk woman aged 40 years and ER positive[b]	–(0)	Dom (0)	£1,730 (0.66)	£24,107 (0.34)
Average risk woman aged 60 years and ER positive[b]	–(0.23)	Dom (0)	£14,324 (0.74)	£45,918 (0.03)
High risk altering age				
High risk woman aged 40 years and ER negative[c]	–(0)	Dom (0)	£249 (0.12)	£8,770 (0.88)
High risk woman aged 60 years and ER negative[c]	–(0)	Dom (0)	£2,317 (0.21)	£11,195 (0.79)
Low risk altering age				
Low risk woman aged 40 years and ER positive[d]	–(0.01)	Dom (0.02)	£7,151 (0.97)	£70,116 (0)
Low risk woman aged 60 years and ER positive[d]	(1)	Dom (0)	Dom (0)	£539,470 (0)
One-way sensitivity analyses[e]				
Treatment effects				
Chemotherapy treatment effects are time dependent[f]	–(0)	Dom (0)	£1,219 (0.23)	£12,128 (0.77)
All chemotherapy treatment effects maintained for 2 years	–(0.36)	Dom (0.06)	£17,383 (0.58)	£163,464 (0)
All chemotherapy treatment effects maintained for 5 years	–(0)	Dom (0)	£2,031 (0.72)	£25,785 (0.28)
All chemotherapy treatment effects maintained for lifetime	Dom (0)	Dom (0)	- (0.13)	£7,943 (0.87)
Treatment effect for FEC-D estimated from TACT only[g]	–(0)	Dom (0)	£603 (0.66)	£31,220 (0.34)
Toxicity related mortality				
No chemotherapy-related deaths	–(0)	Dom (0)	£615 (0.28)	£13,616 (0.72)
High risk of chemotherapy related death (2%)	–(0)	£530 (0)	£580 (0.28)	£14,094 (0.72)
Health related quality of life				
Decrement with chemotherapy equal for all regimens (–0.057) and does not continue beyond treatment	–(0)	Dom (0)	£588 (0.24)	£12,996 (0.76)
HRQoL returns to age-adjusted population norm levels for women surviving 15 years post-recurrence	–(0)	Dom (0)	£624 (0.29)	£14,178 (0.71)

Dom – strategy is dominated, that is it has lower QALYs and greater costs than another strategy or a combination of other strategies.

[a] Cost effectiveness acceptability curves showing results for a wider range of cost-effectiveness threshold values can be found in web Appendix 1.

[b] Average risk women have one positive lymph node and grade 2 tumours 3 cm in size.

[c] High risk women have four positive lymph nodes, and grade 3 tumours 4 cm in size.

[d] Low risk women are axillary lymph node negative with grade 1 tumours 2 cm in size.

[e] Shown for the reference-case cohort.

[f] Analysis utilises the following time dependent annual recurrence rate ratios for CMF chemotherapy in women <50 years of age: years 0–1 = 0.52, (SE = 0.05), years 2–4 = 0.69 (SE = 0.06), years 5–9 = 0.79 (SE = 0.08).[1]

[g] Hazard ratio for DFS with FEC-D from the TACT trial is 0.95 (95% CI: 0.85–1.08).[3]

women surviving 15 years post-recurrence. The impact of changes to the magnitude of the treatment effect for FEC-D was also explored. In this analysis, the base-case treatment effect estimate for FEC-D (Table 2) was replaced with the treatment effect estimate from TACT (HR for disease free survival = 0.95 (SE = 0.06)), the largest and most recent trial of sequential docetaxel and one undertaken in the UK.[3]

Finally, and because the European patent for docetaxel expired in November 2010, threshold analysis was conducted to determine the price to which the drug would need to fall in order for FEC-D to be the most cost-effective treatment strategy (assuming a threshold of £20,000 per QALY) for all patient sub-groups modelled.[29] Further sensitivity analyses are reported in web Appendix 1.

3. Results

3.1. *Reference case cohort*

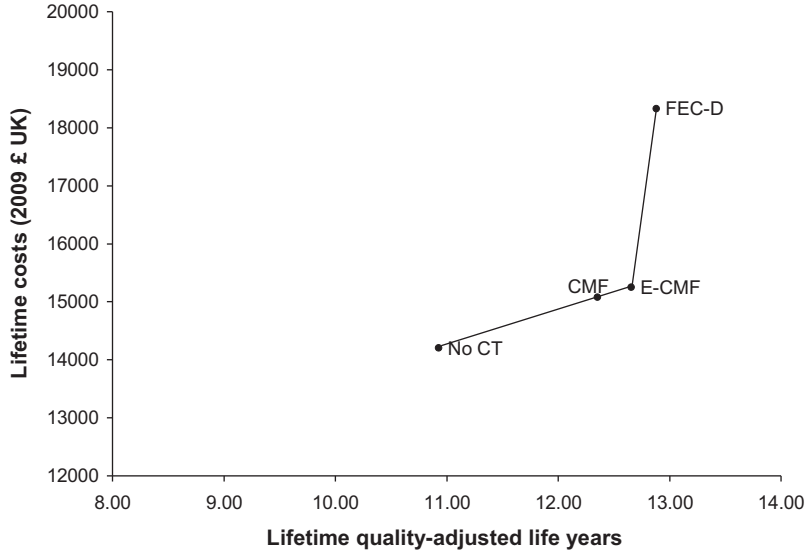
For the reference-case cohort (for whom the predicted probability of remaining recurrence free out to 10 years in the absence of chemotherapy and (given the ER negative status of the group) anti-hormone therapy is 44%), expected costs and QALYs estimated for the four treatment strategies are shown in Table 3 and Fig. 3. FEC-D on average generates the greatest amount of health gain but also has the greatest cost. When compared with E-CMF/FEC60 (the next most effective alternative) the expected lifetime incremental costs and QALYs with FEC-D are £3,081 and 0.225 respectively, giving an ICER of £13,704. This value is less than the standard threshold employed by NICE (of between £20,000 and £30,000 per QALY) indicating that on average, for this patient group, FEC-D is the most cost-effective treatment strategy.

If the threshold is £20,000 per QALY then the probability that FEC-D is cost-effective is 0.72, rising to 0.85 for a threshold of £30,000 per QALY.

3.2. *Sub-group analysis*

Table 4 shows the ICER for each strategy compared with its next best alternative and the probability that each strategy is cost-effective at a threshold of £20,000 per QALY (results for other threshold values are shown in web Appendix 1), for the various sub-groups considered. Given below in parentheses alongside the results for each sub-group examined is the predicted probability of remaining recurrence free out to 10 years (recurrence free survival – RFS) in the absence of chemotherapy and the presence of other routinely administered adjuvant therapies (i.e. radiotherapy and anti-hormone therapy for ER positive patients). Taking the reference cohort first, FEC-D remained cost-effective when patient age was increased from 40 to 60 years (10-year RFS of 50%). Switching ER status from negative to positive increased the ICER for FEC-D versus E-CMF/FEC60 in younger women to £24,107, suggesting that a decision about the most cost-effective regimen would be finely balanced (10-year RFS of 65%). For ER positive older women the ICER for FEC-D exceeded £30,000 per QALY and E-CMF/FEC60 is cost-effective at conventional thresholds (10-year RFS of 77%).

For women considered high risk for recurrence FEC-D was the optimal treatment strategy and this remained the case when patient age was increased from 40 (10-year RFS of



	No chemotherapy	CMF	E-CMF/ FEC60	FEC-D
Incremental cost-effectiveness ratio	--	Dominated	£603	£13,704

Fig. 3 – Expected discounted lifetime costs and QALYs and cost-effectiveness for the reference-case cohort (age 40, 1 positive node, with a 3 cm, grade 2, ER negative tumour – predicted probability of remaining recurrence free at 10-years in absence of chemotherapy and anti-hormone therapy of 44%).

18%) to 60 years (10-year RFS of 22%). For younger low risk women (10-year RFS of 85%) the ICER for FEC-D exceeded £70,000 per QALY, and E-CMF/FEC60 was the most cost-effective strategy. For older low risk women (10-year RFS of 92%) a policy of no chemotherapy was most cost-effective, proving to be less costly and associated with better quality of life than both CMF and E-CMF/FEC60. The ICER for FEC-D versus no chemotherapy in this group exceeded £539,000 per QALY.

Fig. 4a and b further explore, for ER negative and positive patients respectively, the potential for cost-effectiveness to vary by baseline prognosis and age. In both figures, the ICER for FEC-D versus E-CMF/FEC60 increases (FEC-D becomes less cost-effective) as baseline prognosis improves (baseline prognosis is the probability of remaining recurrence free out to 10 years in the absence of chemotherapy, as predicted by the model on the basis of established prognostic factors plus other routinely administered adjuvant therapies (i.e. radiotherapy, and anti-hormone therapy for ER positive women)). Assuming a cost-effectiveness threshold of £20,000 per QALY, Fig. 4a and b can be used to infer the baseline prognosis

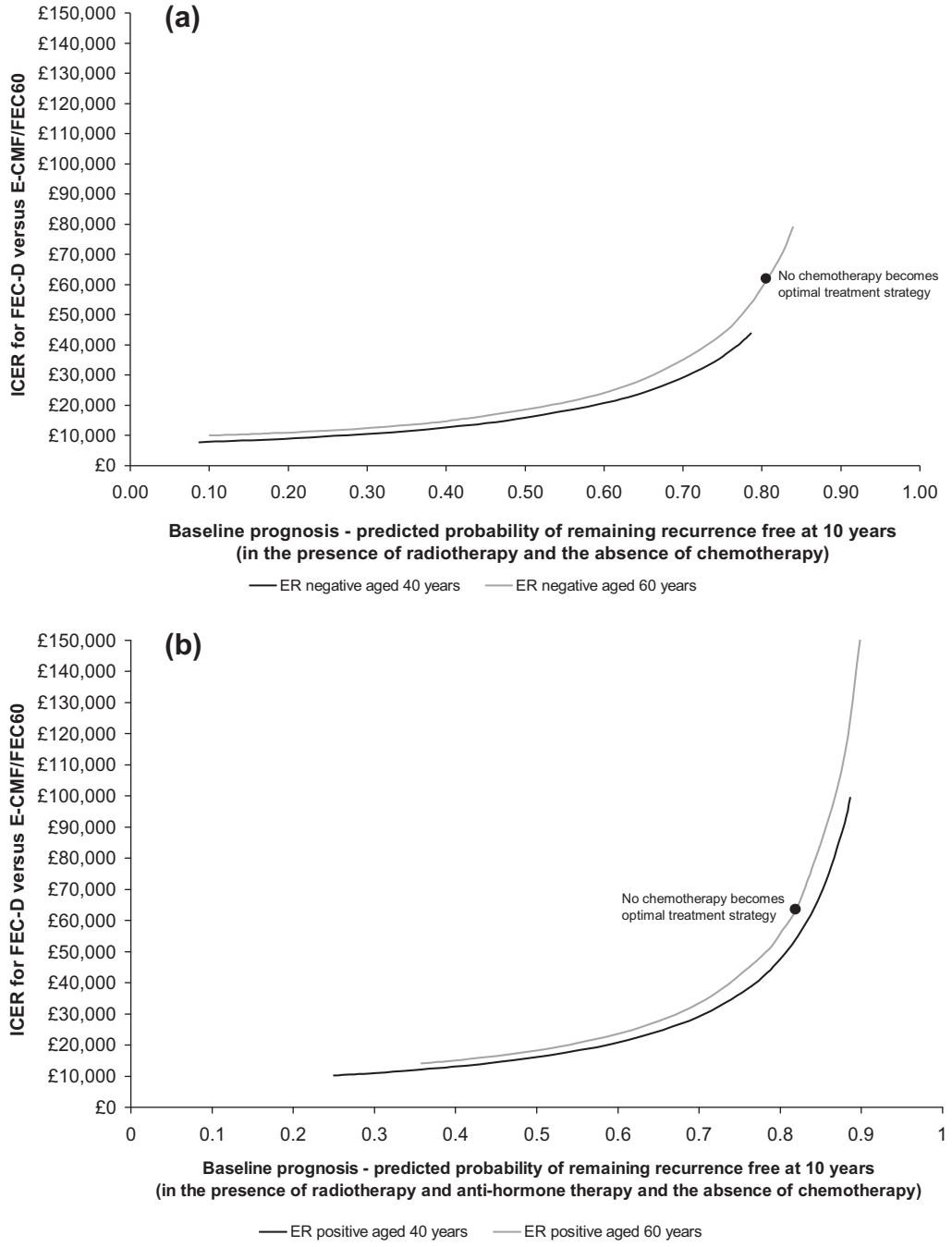


Fig. 4 – Incremental cost-effectiveness ratio (ICER) for FEC-D versus E-CMF plotted against baseline prognosis and by age group, for ER negative (a) and ER positive (b) patients*. * ER positive women aged 40 years are assumed to receive five years of anti-hormone therapy with tamoxifen. ER positive women aged 60 years are assumed to receive five years of anti-hormone therapy with an aromatase inhibitor.

beyond which FEC-D is unlikely to be cost-effective (i.e. the ICER exceeds the £20,000 threshold). The figures show that within each age group, the baseline prognoses at which the most cost-effective treatment switches from FEC-D to E-CMF/FEC60 is similar for ER negative and ER positive patients. For 40 year old ER negative women, for example (Fig. 4a), FEC-D is likely to be cost-effective until baseline prognosis exceeds 59%. For 40-year old ER positive women (Fig. 4b), baseline prognosis must exceed 60% before FEC-D is unlikely to be cost-effective. For older women, in whom chemotherapy is less effective, FEC-D is likely to be cost-effective until baseline prognosis exceeds 53% in ER negative patients (Fig. 4a) and 54% in ER positive patients (Fig. 4b). Also indicated in Fig. 4a and b are the 10-year probabilities of remaining recurrence free in the absence of chemotherapy, at which E-CMF/FEC60 is replaced by 'No chemotherapy' as the optimal treatment strategy for older women. For no patient subgroup was CMF ever the cost-effective alternative.

3.3. *Sensitivity analysis*

Table 4 shows that, for the reference cohort, using time dependent chemotherapy treatment effects had little impact upon the results. Other analyses showed FEC-D would not be cost-effective if chemotherapy reduced the risk of recurrence for just the first 2 years following surgery (the effect ceasing thereafter) (ICER = £163,464), but would be highly cost-effective if the treatment effect was maintained over a patient's lifetime (ICER = £7,943). Running the model using the hazard ratio for FEC-D versus E-CMF/FEC60 for disease free survival, reported by the TACT trial, increased the base-case ICER for FEC-D to £31,220.

Threshold analysis showed that, for ER positive women aged 40 years and with an average risk of recurrence, the price of docetaxel would need to fall from £1232 per cycle to £1075 per cycle in order for FEC-D to replace E-CMF/FEC60 as the optimal treatment strategy. For ER positive women aged 60 years the price would need to fall to £700 per cycle. For low risk ER positive women aged 40 years, the price fall required was even greater, from £1232 to £540 per cycle. FEC-D was never cost-effective for low risk ER positive women aged 60 years, even when the price of docetaxel was reduced to £0.

4. Discussion

This study used decision analytic modelling to estimate and compare the lifetime costs and effects of no chemotherapy and first, second, and third generation adjuvant chemotherapy for women with early breast cancer. Sub-group analyses showed different treatment strategies have the potential to be cost-effective for different types of patients. Assuming the cost-effectiveness threshold to be £20,000 per QALY, and summarising for younger women first, FEC-D appears cost-effective for patients, who, on the basis of their prognostic factors and other adjuvant therapies administered (radiotherapy, and in the case of ER positive women, tamoxifen) have a 10-year predicted probability of remaining recurrence free in the absence of chemotherapy of less than 59–60%. Above this range E-CMF/FEC60 appears to be the cost-effective alternative. Amongst older women, FEC-D appears cost effective for patients, who, on the basis of their prognostic factors and other adjuvant therapies (radiotherapy, and in the case of ER positive women, an aromatase inhibitor) have a 10-year predicted probability of remaining recurrence free in the absence of chemotherapy of less than 53–54%. Above this range, E-CMF/FEC60 is the cost-effective alternative up until predicted 10-year recurrence free survival exceeds around 80% (Fig. 4a and b), at which point a policy of no chemotherapy becomes optimal.

One-way sensitivity analyses demonstrated the model's results to be robust to changes in the risk of chemotherapy-related mortality and the impact of adjuvant therapy on HRQoL. Results were sensitive, however, to the duration and magnitude of chemotherapy treatment effects. In particular, replacing the pooled treatment effect estimate for FEC-D versus E-CMF/FEC60 from the TACT and PACS 01 trials with the treatment effect estimate from the TACT trial alone (the largest study and one undertaken in the UK), increased the ICER for FEC-D in the reference-case cohort from £13,704 to £31,220. As the newest of the three regimens compared here, the evidence base for FEC-D is limited. Furthermore the two RCTs contributing effectiveness data to this study reported variable findings – PACS01 finding in favour of FEC-D (HR for DFS = 0.80, 95% CI 0.67–0.96), TACT showing less favourable results (HR for DFS = 0.95, 95% CI 0.85–1.08).[2,3] Further consideration of the evidence on the effectiveness of FEC-D is clearly required and, until these data become available, the results reported in this paper should be interpreted with caution.

In anticipation that the cost of docetaxel will fall following its patent expiration, threshold analysis was used to identify the cost of the drug at which FEC-D would become cost-effective for various sub-groups shown in Table 4. For some groups the cost reduction required was small (for example £157 per cycle for young women with ER positive tumours and an average risk of recurrence). For others (older women with ER positive tumours and a low risk of recurrence) the model suggested that FEC-D was unlikely to be cost-effective, even if the cost of docetaxel was zero. This was because the incremental cost of FEC-D over no chemotherapy (attributable to docetaxel-related adverse events) remained substantial in relation to the small QALY gain received by this low risk group.

This study has a number of strengths. The 'prognostic' model used to predict the risk of a first recurrent event in the absence of anti-hormone therapy and chemotherapy showed a high degree of consistency with the results of the ABC and TACT trials (see web Appendix 1). Despite its widespread use by clinicians in the UK, Adjuvant! Online was not used to generate the prognosis predictions for the health economic model.[30] Adjuvant!, a web-based prognosis prediction algorithm developed in the United States, provides information on the 10-year cumulative risk of recurrence, rather than annual risks over a lifetime horizon as required by the disease modelling here. Furthermore, recent evidence is available to suggest that Adjuvant! Online may over-estimate prognosis (overall and breast cancer specific survival) for women with early breast cancer in the UK.[31]

In populating the model, it was possible to draw upon individual patient data captured during the ABC, NEAT and TACT

RCTs. All three trials elicited information on HRQoL from patients during and immediately following chemotherapy; the EQ-5D data collected during ABC and TACT have not previously been published. Such data are traditionally scarce, as illustrated by the need for many economic models of adjuvant therapy to rely upon expert clinical opinion or simple assumption as the source of their HRQoL estimates.[32–36] Here, analyses of trial data not only provided estimates of the decrements in HRQoL experienced during chemotherapy treatments, but also indicated that the negative effect of treatments continued for at least a further year. This is a novel finding which, to our knowledge, has not been incorporated in any previous economic analysis in this field.

The study is, of course, not without its limitations. The chemotherapy regimens evaluated were those specifically investigated by three large UK-led RCTs and so may not necessarily reflect routine practice elsewhere. This is particularly likely to be the case with FEC-D, a regimen which is not currently licensed for use in the UK. Decision makers will need to determine whether the results reported here are likely to be generalisable to their own settings.

One must also acknowledge that whilst breast cancer is a complex and evolving disease, decision models are essentially simplifications. Assumptions inevitably have to be made and inputs based upon data available at the time of analysis. With evidence of improving prognoses over the last 3 decades and with the longer-term follow-up of patients likely to generate new information on the ways in which the disease and indeed adjuvant chemotherapy can affect different types of women, implications for the work presented here must be considered. Firstly, and in relation to improved prognoses, it could be argued that predictions of the risk of recurrence within our study may now be unrepresentative, as the Oxford Churchill Hospital dataset which informed this modelling contained patients treated between 1986 and 2001. Given that the model was able to accurately predict recurrence free survival for patients in both the ABC and TACT trials (see web Appendix 1), we would suggest this is not the case. However, for readers for whom this is a concern, Fig. 4a and b provide a facility for reading off cost-effectiveness results for lower levels of risk. Secondly, it is possible that the effects of chemotherapy are modified by factors in addition to patient age (for example by ER status); as such evidence becomes available, the model and its results could easily be amended to incorporate these further treatment interactions.

Although the ABC, NEAT, and TACT trials were largely conducted before the widespread use of adjuvant anti-HER-2 therapy, it is necessary to consider the potential implications of the use of HER-2 expression as a prognostic factor and prediction of response to anti-Her-2 therapy. Simplistically, in the adjuvant setting the use of trastuzumab neutralises the adverse prognostic effect of HER-2 overexpression. Time will tell if the promising reduction in recurrence with adjuvant trastuzmab in early analyses translate into long term survival benefits of a similar magnitude. As we assume that all HER-2 overexpressing tumours will now receive appropriate adjuvant anti-HER-2 therapy – we have not included HER-2 expression in the model. For metastatic disease, the cost of anti-HER-2 treatment (in combination with paclitaxel) can exceed £25,000 per annum, thereby adding substantially to treatment costs post-recurrence.[37] By preventing more of these recurrences, and thereby the need for health care providers to purchase anti-Her-2 therapy to treat recurrent disease, adjuvant chemotherapy may appear more cost-effective than shown here. Further research is warranted to determine the net impact of trastuzumab for advanced breast cancer, on the results presented here.

5. Conclusion

This paper has presented the first known comparison of the cost-effectiveness of three different generations of adjuvant chemotherapy for early breast cancer patients with differing prognoses. The results are necessarily complex, with cost-effectiveness shown to vary not only with the underlying risk of a recurrence, but also according to age and ER status. The findings are also subject to uncertainty, particularly in relation to the effectiveness of FEC-D, a parameter on which further research is clearly required.

At a time when health care resources are particularly scarce and there is a need to identify and target increasingly expensive therapies towards those patients for whom the benefits justify the costs, our findings, based upon best available data, should prove useful for decision makers formulating cost-effective adjuvant chemotherapy treatment protocols in the field of early breast cancer.

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Individual contributions

HC developed, populated, and analysed the economic model and drafted the manuscript. DE assisted in the development of the economic model, conducted analyses of trial data for use in the model, and helped draft the manuscript. DB was the clinical lead for the project, provided input into the modelling process, helped write the manuscript, and co-ordinated manuscript circulation across the authorship. SG advised on the development and population of the economic model and provided comments on multiple versions of the manuscript. AM provided technical advice on economic model development and population and provided feedback on the manuscript. MS secured funding for the study, co-ordinated the work, advised on all aspects of the modelling, and commented upon all drafts of the manuscript produced. AG and AH supervised HC during the development of the prognostic model, and provided comments on the manuscript. JB, HE, PH, LJ, PBL, DC, JY, CP, LH, JD, and PE, provided comments on the manuscript and were pivotal in the design and conduct of the clinical trials on which the analysis was based.

Conflict of interest statement

HC had access to all data used in this study and had final responsibility for the decision to submit the paper for

publication. DB received educational travel grants from Roche and Astra-Zeneca. DC received research funding, honoraria, consultancies and travel grants from Pfizer and Sanofi-Aventis. PBL in the past received an honorarium for roles on Advisory boards of Sanofi-Aventis and Pfizer. HE has received unrestricted educational grants for research trials from Pfizer (epirubicin), and Sanofi-Aventis (docetaxel). MS is a director and minority shareholder of a consultancy company which undertakes work for pharmaceutical companies. He has not personally been involved in consultancy projects relating to the chemotherapy regimens evaluated in this study.

Role of funding source

The funding source had no involvement in the study design or analysis, the interpretation of the results, the writing of the paper, or the decision to submit for publication.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.ejca.2011.06.019.

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